

## Fluoroquinolones: Mechanism of Action, Classification and Phototoxicity

Jyoti Singh<sup>1\*</sup>, Ajeet K Srivastav<sup>2,3</sup>, Divya Dubey<sup>2</sup> and Shikha Agnihotry<sup>4</sup>

<sup>1</sup>Academy of Scientific and Innovative Research (AcSIR), CSIR-Human Resource Development Centre (CSIR-HRDC), Ghaziabad, Uttar Pradesh, India

<sup>2</sup>School of Dental sciences, Department of Biochemistry, Babu Banarasi Das University, BBD City, Faizabad Road, Lucknow- 226001, Uttar Pradesh, India

<sup>3</sup>Redcliffe Hygiene Private Limited, 2nd Floor, Plot No. 517, Go Hive, Udyog Vihar Phase -3, Gurugram, Haryana 122016, India

<sup>4</sup>Department of Computational Biology and Bioinformatics, Jacob Institute of Biotechnology and Bio-Engineering, Sam Higginbottom University of Agriculture, Technology and Sciences, Allahabad-211007 (U.P.), India.

Received April 26, 2020; Revised June 08, 2020; Accepted June 10, 2020

### ABSTRACT

Fluoroquinolones shows broad spectrum of activity against gram negative and gram-positive bacteria by binding to bacterial topoisomerase and inhibiting the bacterial DNA synthesis. They are highly useful in the treatment of various types of infectious disease like respiratory tract infection, urinary tract infection, bacterial skin infection and different tissue infection. Since several decades' quinolones use for infectious disease, nalidixic acid was first generation fluoroquinolones, since then a number of new fluoroquinolones came in the market various structural modifications and increase action spectrum activity. At the same time different type of adverse effects of fluoroquinolones on gastrointestinal tract (gi), central nervous system (CNS), nephrotoxicity, tendinitis and phototoxicity are also reported. Photosensitizing properties are one of its drawbacks of this drug skin. Fluoroquinolones under the ultraviolet radiation exposure induce the formation of photoactivated molecule like singlet oxygen, superoxide anion radicals and hydrogen peroxide, which possess the tendency to alter biological systems and generating harmful effects like phototoxicity (erythema, pigmentation change, and ocular toxicity), photocarcinogenicity, and photoallergy. In this review we summarize the action mechanism, classification of fluoroquinolones, with its reported study of photoallergy, phototoxicity and photomutagenesis mediated by fluoroquinolones. We have discussed the role of reactive oxygen species scavenger in minimizing harmful effects of these photosensitive drugs.

**Keywords:** Fluoroquinolones, Phototoxicity, Photogenotoxicity

### INTRODUCTION

The term photosensitization is connected with phototoxic and photoallergic reactions in skin which are mainly visualized by systematic administration or topical application of phototoxic chemical/drug. Chemical phototoxicity is an adverse human skin reaction induced by the combined effect of exogenous chemical agents (for example drugs, hair dye, sunscreen and food preservatives) and light, mainly the exposure of visible (400-700 nm) and ultraviolet (UV) A and B (320-400 nm and 290-320 nm, respectively) wavelengths. Several features such as absorption and metabolism of phototoxic compound also affect the individual's response to photosensitive agents. Amount of light penetration in skin also influences the phototoxic effect because it differs among individuals due to the genetic and environmental factors. Fluoroquinolones are used for intra-abdominal infections and community-acquired pneumonia type infectious disease. Scientists have reported that 10% of patients receiving fleroxacin,

lomefloxacin and sparfloxacin are known to be significantly photosensitized while ciprofloxacin, enoxacin, norfloxacin and ofloxacin have been reported to be less phototoxic. In a control study on Caucasian people, it was found that sparfloxacin induced clinically phototoxicity effect while levofloxacin and sitafloxacin failed to exert significant adverse effect.

**Corresponding authors:** Dr. Jyoti Singh, AcSIR, CSIR-Human Resource Development Centre (CSIR-HRDC), Ghaziabad, Uttar Pradesh, India, E-mail: jsjyoti156@gmail.com

**Citation:** Singh J, Srivastav AK, Dubey D & Agnihotry S. (2020) Fluoroquinolones: Mechanism of Action, Classification and Phototoxicity. J Pharm Drug Res, 3(4): 405-414.

**Copyright:** ©2020 Singh J, Srivastav AK, Dubey D & Agnihotry S. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Pharmacokinetics and pharmacodynamic properties of fluoroquinolones

The new fluorinated quinolones have a good pharmacokinetic profile with broader action spectra, as compared to previous version of fluoroquinolones [1]. Fluoroquinolones can be taken in two forms i.e. orally & intravenous, but it is known that they are well absorbed by oral administration, with maximum plasma concentration ( $C_p$  max) within few hours of administration and consequently gets accumulate in some of the vital organs like GI tract, kidney and liver. Fluoroquinolones are highly bioavailable for example the bioavailability of gemifloxacin is 70% and about 99% for levofloxacin [2]. Another study reported that the absolute bioavailability of gatifloxacin is 96% [3]. Some of the fluoroquinolones exhibit fast diffusion into alveolar macrophages, bronchial mucosa saliva and are also highly available in serum [4]. Fourth generation fluoroquinolones in comparison to former generation fluoroquinolones, like trovafloxacin and moxifloxacin, exhibit increased plasma concentration, better tissue penetration and longer elimination time [5]. Protein binding has a role in antimicrobial activity and it is clinically significant [6]. It was also found that fourth generation fluoroquinolones have higher protein binding ability than the third generation. All fluoroquinolones are eliminated by either renal or hepatic mode, such as levofloxacin, Ofloxacin, undergo renal elimination whereas, sparfloxacin, gatifloxacin, moxifloxacin, undergo hepatic metabolism [7].

### Action Mechanism of Fluoroquinolones

Fluoroquinolones are known to inhibit the function of two essential enzymes DNA topoisomerase IV and DNA gyrase, involved in bacterial DNA replication. Cytotoxicity induced by fluoroquinolones in bacterial cell is a two-step process. Firstly, an irreversible complex of topoisomerases-

quinolone-DNA is formed and secondly, the topoisomerase activity is inhibited by breaking bonds in double stranded DNA [8]. Fluoroquinolones interact with the enzyme-bound DNA complex to create conformational changes that result in the inhibition of normal enzyme activity. As a result, the new drug-enzyme-DNA complex block progression of the replication fork, thereby reducing normal bacterial DNA synthesis and finally resulting in rapid bacterial cell death. DNA gyrase is the primary target for quinolones activity which was identified in *E. coli*. [9]. DNA Gyrase initiates negative super helical twists in the bacterial DNA double helix ahead of the replication fork, thereby catalyzing the separation of daughter chromosomes. This process is important for initiation of DNA replication. DNA Gyrase is composed of two monomeric subunits i.e. *GyrA* and *GyrB*, which are encoded by the *gyrA* and *gyrB* genes, respectively [10]. Topoisomerase IV is a secondary target for activity of quinolones which are responsible for removing the interlinking of daughter chromosomes, thereby allowing segregation into two daughter cells at the end of a round of replications (Figure 1) [11]. Topoisomerase IV is similar to gyrase which is made of two subunit- *ParC* and *ParE*, which identified as *GrlA* and *GrlB*, correspondingly, in *Staphylococcus aureus*. *ParC* is equivalent to *GyrA*, and *ParE* is equivalent to *GyrB*. Resistance to fluoroquinolones was usually supposed to be caused by one of two promising mechanisms either by mutation of the topoisomerases enzymes or decrease in intracellular drug concentrations by inducing morphological change in prions channels [12]. New fluoroquinolones act together on DNA gyrase and topoisomerase IV, and the action of these fluoroquinolones, are less affected by double mutations than older fluoroquinolones [13].

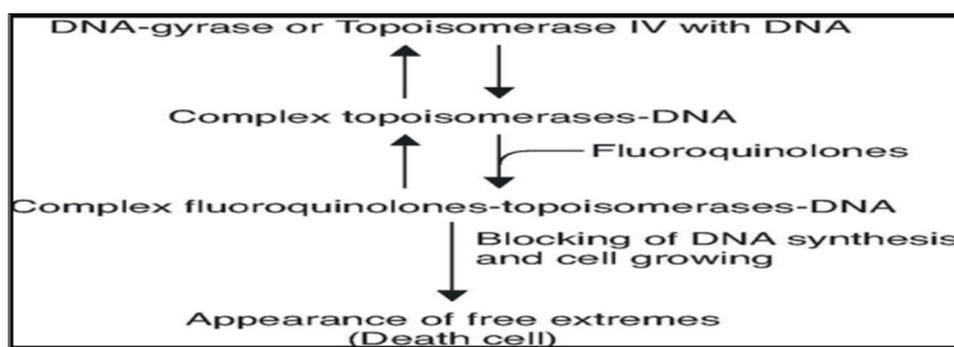


Figure 1. Mechanism of action of fluoroquinolones adapted from Rodríguez (2005).

### Classification of Fluoroquinolones

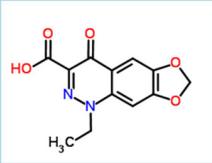
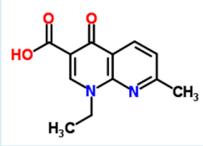
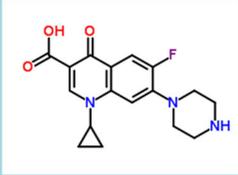
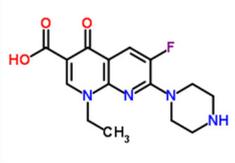
Nalidixic acid (have limited activity toward gram negative bacteria) was developed in 1962 by Lescher and his colleagues. First generation of fluoroquinolones was developed in 1982 with 6 fluorinated derivative (norfloxacin, ofloxacin, ciprofloxacin) which have better

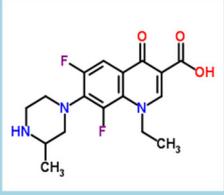
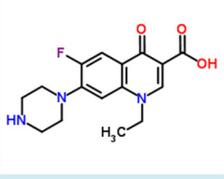
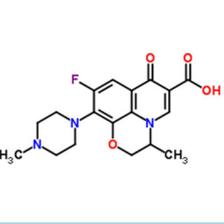
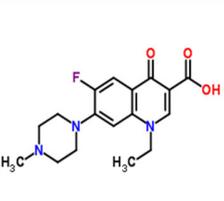
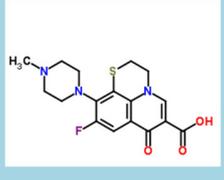
activity against gram negative bacteria [14]. Usually fluoroquinolones were classified on the basis of generation. The antibacterial activity of this drug has been augmented as different generations of quinolones were developed. Second generation quinolones have a moderate effect on gram positive bacteria with improved action spectra towards gram

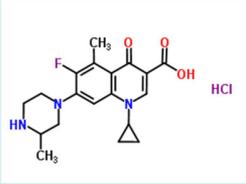
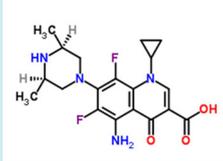
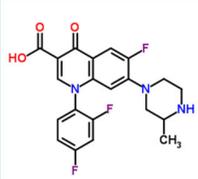
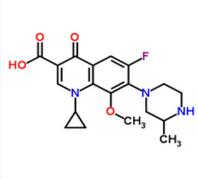
negative bacteria compared to first generation [8]. A third generation has good potency towards anaerobic and gram-positive bacteria especially towards *Pneumococci*. Fourth-generation fluoroquinolones have shown better treatment towards *pneumococci* and anaerobes [15]. Clinical use of second generation was limited because of its poor bioavailability and renal toxicity while the third generation of fluoroquinolones expands its clinical utility in the field of

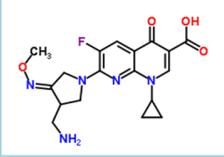
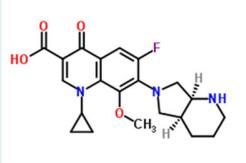
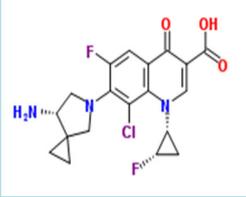
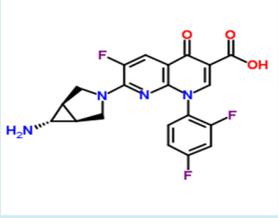
ophthalmology for therapy of eye infection and topical application in bacterial keratitis [16]. Fourth generation quinolones moxifloxacin and gatifloxacin has been approved by FDA for topical application because of their dual mechanism of action towards the gram positive and gram-negative bacteria [17]. In **Table 1** we have discussed about the classification of different generation of fluoroquinolones.

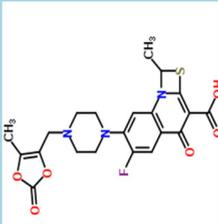
**Table 1.** List of Different Generation of Quinolones.

Generations and Characteristics	Agent	Brand Name	Chemical Structure	Undesirable
<b>Generation-I</b> Treatment of urinary tract infections	Cinoxacin*	Cinobac	 <p>(1,3) Dioxolo(4,5-g) cinnoline-3-carboxylic acid, 1-ethyl-1,4-dihydro-4-oxo-</p>	<b>Phototoxicity,</b> Hypersensitivity
	Nalidixic acid#	NegGram, Wintomylon	 <p>1,8-Naphthyridine-3-carboxylic acid, 1-ethyl-1,4-dihydro-7-methyl-4-oxo-</p>	<b>Phototoxicity,</b> Hyp ersensitivity
<b>Generation- II</b> Enhanced activity, mainly against gram-negative pathogens; limited potency against gram-positive Pathogens	Ciprofloxacin*	Alcipro, Ciprobay, Cipro, Ciproxin	 <p>1-Cyclopropyl-6-fluor-4-oxo-7-(1-piperazinyl)-1,4-dihydro-3-chinolincarbonsäure</p>	allergic reaction, pruritus, urticaria, <b>photosensitivity/p</b> <b>hototoxicity</b>
	Enoxacin#	Enroxil, Penetrex	 <p>1,8-Naphthyridine-3-carboxylic acid, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-</p>	Inhibition of cytochrom p450

	Lomifloxacin*	Maxaquin	 <p>1-Ethyl-6,8-difluoro-7-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid</p>	<b>Phototoxicity</b>
	Norfloxacin*	Lexinor, Noroxin, Quinabic, Janacin	 <p>1-Ethyl-6-fluor-4-oxo-7-(1-piperazinyl)-1,4-dihydroquinolinecarbonsäure</p>	Skin inflammation, skin rashes, muscle weakness.
	Ofloxacin*	Floxin, Oxaldin, Tarivid	 <p>(±)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido(1,2,3-de)-4-benzoxazine-6-carboxylic acid</p>	Tendinopathy, central nervous system <b>photosensitivity/p hototoxicity</b>
	Pefloxacin*	Peflacin	 <p>1-Ethyl-6-fluor-7-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-3-chinolincarbonsäure</p>	Tendinopathies, <b>phototoxicity</b>
	Rufloxacin*	Uroflox	 <p>7H-1,4-Thiazino[2,3,4-ij]quinoline-6-carboxylic acid, 9-fluoro-2,3-dihydro-10-(4-methyl-1-piperazinyl)-7-oxo-</p>	<b>Photosensitivity,</b> Skin rashes

<p><b>Generation- III</b> Balanced broad spectrum of activity; increased potency against pneumococci gram positive bacteria</p>	<p>Grepafloxacin*</p>	<p>Raxar</p>	 <p>1-Cyclopropyl-6-fluor-5-methyl-7-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydroquinolincarbonsäure</p>	<p>Prolongation Qc interval, <b>phototoxicity</b>, hyperlipidemia</p>
	<p>Levofloxacin*</p>	<p>Cravit, Levaquin</p>	 <p>(3S)-9-Fluoro-3-methyl-10-(4-methyl-1 piperazinyl)-7-oxo-2,3-dihydro-7H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid</p>	<p><b>Photosensitive</b>, Skin reaction, purple skin rashes, Insomania</p>
	<p>Sparfloxacin*</p>	<p>Zagam</p>	 <p>5-Amino-1-cyclopropyl-7-[(3R,5S)-3,5-dimethyl-1-piperazinyl]-6,8-difluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid</p>	<p><b>Phototoxicity</b> and Qt prolongation</p>
	<p>Temafloxacin*</p>	<p>Omniflox</p>	 <p>1-(2,4-Difluorophenyl)-6-fluoro-7-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-3 quinolinecarboxylic acid</p>	<p>Heamolytic uremic syndrom</p>
<p><b>Generation- IV</b> Markedly enhanced activity against Gram-positive bacteria</p>	<p>Gatifloxacin*</p>	<p>Zigat, Tequin</p>	 <p>1-Cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid</p>	<p>QTc interval prolongation hepatotoxicity</p>

	Gemifloxacin	Factive	 <p>7-[(4Z)-3-(Aminomethyl)-4-(methoxyimino)-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid</p>	<p><b>Photosensitivity,</b> QTc interval prolongation, Nervous System Disorder</p>
	Moxifloxacin*	Avelox, Vigamox	 <p>1-Cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid</p>	<p>Hepatotoxicity, Insomnia</p>
	Sitafloxacin*	Gracevit	 <p>7-[(7S)-7-Amino-5-azaspiro[2.4]hept-5-yl]-8-chloro-6-fluoro-1-[(1R,2S)-2-fluorocyclopropyl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid</p>	<p><b>Phototoxicity</b></p>
	Trovafloxacin#	Trovan	 <p>7-(6-Amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid</p>	<p>Hepatotoxicity, CNS effect</p>

	Prulifloxacin*	Quinson	 <p>6-Fluoro-1-methyl-7-{4-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl]-1-piperazinyl}-4-oxo-4H-[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid</p>	Facial edema, <b>Phototoxicity</b>
--	----------------	---------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------

QTc=Corrected Q-T interval, CNS= central nervous system

#Naphthyridone derivative of quinolones

\*Fluoroquinolones derivative of quinolones

### Structure Phototoxicity Relationship of Fluoroquinolones

Quinolones are obtained as a residue during the development of quinine and represent a basic pharmacore of fluoroquinolones [18]. First structural modification was introduced in fluoroquinolones by adding fluorine atom at C-6 position [19]. This single modification enhances its potency towards gyrase inhibition by 10-fold and increases its MIC near about 100-fold. Two major groups have been derived from quinine i.e. quinolones and naphthyridones. Quinolones possess carbon or hydrogen atom at C-8 position while naphthyridones have a nitrogen atom at the same position, structural modification of basic pharmacore has increased rapidly now a day's because it improved its clinical utilization [20]. Its activity was further enhanced by the addition of some other groups on N-1, C-1 and C-7 position of the basic structure of quinolones (Figure 2). Piperazine group which is situated at C-7 position showed improved activity toward gram negative bacteria including *Pseudomonas* species by preventing efflux mechanism of bacterial cell [21]. There is some position on the basic pharmacore where structure modification rarely introduced, including C-2, C-3 and C-4 where Position 3 and 4 are responsible for binding of fluoroquinolones with DNA topoisomerase, therefore, 3-carboxylic and 4-carbonyl is a very essential site for antimicrobial activity [22]. Position-2 is very close to binding site of DNA gyrase so any bulky functional group may inhibit the access point of binding of fluoroquinolones with topoisomerase thereby reduction in the antimicrobial activity occurred [23]. Fluoroquinolones are vulnerable to photodegradation process, which may minimize their antibacterial activity and increase the incidence of side effects like photocytotoxicity [21]. Fluoroquinolone induced phototoxicity is initiated by the absorption of UVA light energy which may lead to a chemical reaction in the body by generating adverse skin reaction. It has been found that 8-halogenated fluoroquinolones harbor more phototoxicity potential [24]. It

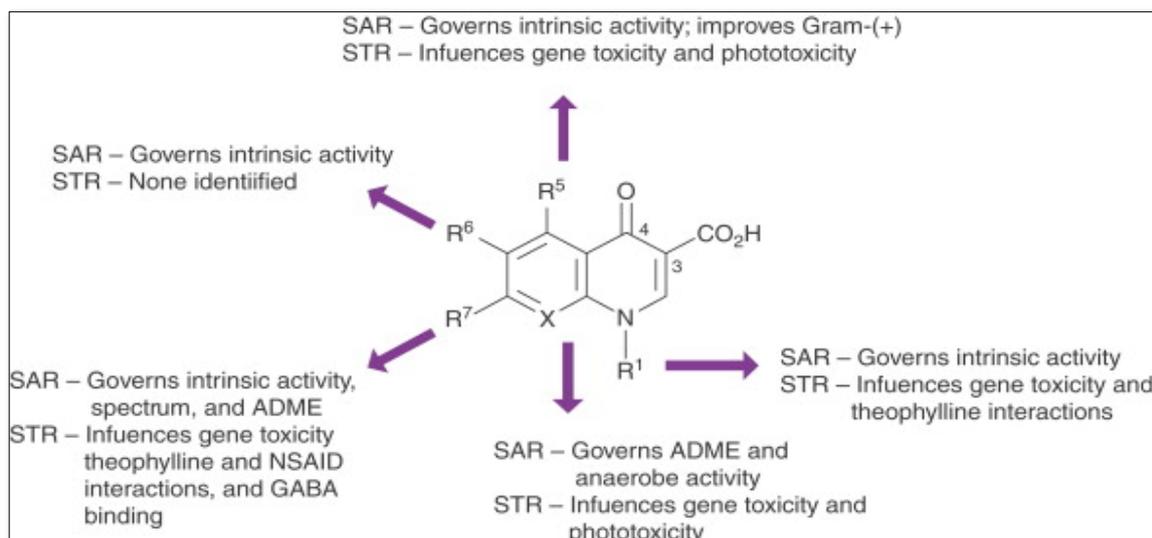
has been investigated that halogen atom at position 8 enhanced the antibacterial activity of fluoroquinolones and bio-availability [25]. However, 8 halogenated fluoroquinolones also have more phototoxic potential and exerts a severe effect on skin (erythema, urticaria pruritus, and rash etc), thereby to minimize this side effects, some fluoroquinolone have been developed that contain methoxy group at 8 position, these fluoroquinolones shown low incidence of phototoxicity in humans or animals in comparison to fluoroquinolones fluorinated at 8 position [26]. Structure phototoxicity relationship were also proved by in vivo experiment in female Balb/c mice where severe auricular lesion was occurred by lomifloxacin and sparfloxacin, that possess the fluorine atom at 8<sup>th</sup> positions while gatifloxacin and ofloxacin induced mild adverse effect.

### Cellular target involved in phototoxicity of fluoroquinolones

Fluoroquinolones harbors Lewis acid-base properties due to which 7-piperazinyl and 3-carboxyl group, dehalogenation of fluoroquinolones occurred by protonation and dissociation of these groups respectively and Pka value of fluoroquinolones is near about 7 which favored its accumulation in lysosomes [27]. Fluoroquinolones easily entered in lysosome in its zwitter ionic form where it is protonated due to acidic PH and trapped in non diffusible form, accumulation of the protonated form of fluoroquinolones are responsible for its detergent like properties and induce lysosomes destabilization [28]. Few studies have revealed the lysosomes are accumulation site of fluoroquinolones drug in fibroblasts, keratinocytes and in epithelial cells [29-31].

### Lysosomes

Lysosomes are membrane bound cell organelle that contains various types of hydrolase enzyme hence its environment is



**Figure 2.** Structure of Quinolones adapted from Dogmala (1994).

acidic mainly responsible for autophagic, phagocytic and endocytotic activity [32]. Lysosome is also one of the possible intracellular targets for UVA mediated sparfloxacin photosensitization on human bucal mucosa cells detected by fluorescence microscopy and microspectrofluorometry [33]. Privileged accumulation of fluoroquinolones like ciprofloxacin, lomefloxacin, norfloxacin and ofloxacin was in epithelial cell lysosomes due to its lysomotrophic nature which was detected by fluorescence confocal microscopy under UV-R induced photopolymerization of the alpha crystalline lens protein and human lens transparency loss occurred [31]. In HS 68 fibroblasts it was found that fluoroquinolones ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin and BAY 3118 localized in lysosomes and also affect other cytoplasmic site other than lysosome during UVA radiation which was detected by fluorochrome dye [29].

### Mitochondria

In cells mitochondria is the most important site for the production of ROS. About 1-2% of the molecular oxygen converted into ROS in mitochondria at complex-I and complex-III of respiratory chain reaction [34] It was reported that photosensitized ofloxacin, norfloxacin, lomefloxacin, ciprofloxacin and BAYy 3118 caused mitochondrial membrane destabilization. However, it is well-known that change in mitochondria membrane permeability is an essential step for apoptosis mediated cell death, to understand the mechanisms of cytotoxicity of two extensively used quinolone antibiotic CPX or NFX and UV light (NFX\*) which induced lysosomal membrane destabilization that was examined by the liberation of cathepsins from lysosomes. Lysosome membrane destabilization induced mitochondrial membrane permeabilization which was detected by the release of

cytochrome c and caused cell death in the caspase independent manner [35].

### Prevention of fluoroquinolones induce phototoxicity

The human body has number of mechanisms to diminish the detrimental effect of ROS, by liberating antioxidants, which are induce either by endogenously or exogenously. It was investigated that when Vitamin E (alpha-tocopherol) quenches the superoxide and singlet oxygen and inhibited 8-oxo-7,8- dihydroguanine (8-oxoGua) in Lomifloxacin induced phototoxicity (Rosen JE 2000). Similarly 1,4-diazabicyclo[2.2.2] octane (DABCO), Superoxide dismutase (SOD) and N-acetyl-cysteine (NAC) suppress the fluoroquinolones induced photosensitization effect in HaCaT cell line [36]. Sodium azide is a selective scavenger of singlet oxygen, it quenches singlet oxygen by charge transfer intermediate and it is also depending on ionic strength of the aqueous system. It has been found that photochemically induce singlet generation by UVR irradiated Fluoroquinolones quenched by NAC.

### CONCLUSION

Since last few decades it has been reported that India is the largest consumer of antibiotic. It has been observed since 2000-2010 use of fluoroquinolones increased significantly in hospital, veterinary and household application. Fluoroquinolones exhibit photomutagenicity and toxicity in the presence of UVR. This toxicity is related to the generation of reactive oxygen species due to oxidative stress. Photosensitivity reaction induced by fluoroquinolones is related to blistering redness, overstate sunburn. Photosensitivity of fluoroquinolones is due to its structure several structural modifications introduce in new generation fluoroquinolones to increase its potential and reduce its toxic effect. Current information about the fluoroquinolones drug

can be used by the drug developer because phototoxicity potential of fluoroquinolones is mainly due to its structure. Dehalogenation is the process by which these drugs show their phototoxicity potential and by altering its chemical structure we can reduce its phototoxic effect. Present review can make people aware about the phototoxic nature of fluoroquinolones and it could be clinically minimized by the avoid the UVR exposure to person after having this drug, especially in peak hours.

## REFERENCES

- Andriole VT (2005) The quinolones: Past, present, and future. *Clin Infect Diseases* 41: S113-S119.
- De Smet J, Colin P, De Paepe P, Ruige J, Batens H, et al. (2011) Oral bioavailability of moxifloxacin after Roux-en-Y gastric bypass surgery. *J Antimicrob Chemother* 67: 226-229.
- Peloquin CA, Hadad DJ, Molino LPD, Palaci M, Boom WH, et al. (2008) Population pharmacokinetics of levofloxacin, gatifloxacin and moxifloxacin in adults with pulmonary tuberculosis. *Antimicrob Agents Chemother* 52: 852-857.
- Zhanell GG, Noreddin AM (2001) Pharmacokinetics and pharmacodynamics of the new fluoroquinolones: Focus on respiratory infections. *Curr Opin Pharmacol* 1: 459-463.
- Reilly RM, McDonald HA, Puttfarcken PS, Joshi SK, Lewis L, et al. (2012) Pharmacology of modality-specific transient receptor potential vanilloid-1 antagonists that do not alter body temperature. *J Pharmacol Exp Ther* 342: 416-428.
- Aminimanizani A, Beringer P, Jelliffe R. (2001) Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. *Clin Pharmacokinet* 40: 169-187.
- Woodhead JD, Hergt JM (2005) A preliminary appraisal of seven natural zircon reference materials for in situ Hf isotope determination. *Geostand Geoanal Res* 29: 183-195.
- Bolon MK (2011) The newer fluoroquinolones. *Med Clin N Am* 95: 793-817.
- Drlica K, Malik M, Kerns RJ, Zhao X (2008) Quinolone-mediated bacterial death. *Antimicrob Agents Chemother* 52: 385-392.
- Singhal R, Reynolds PR, Marola JL, Epperson LE, Arora J, et al. (2016) Sequence Analysis of Fluoroquinolone Resistance-Associated Genes *gyrA* and *gyrB* in Clinical Mycobacterium tuberculosis Isolates from Patients Suspected of Having Multidrug-Resistant Tuberculosis in New Delhi, India. *J Clin Microbiol* 54: 2298-2305.
- Ketron AC, Aldred KJ, Lindsey RH, Osheroff N (2015) Gyrase and Topoisomerase IV as Targets for Antibacterial Drugs. *Molecular Life Sciences: An Encyclopedic Reference*, pp: 1-5.
- Jacoby GA (2017) Plasmid-mediated quinolone resistance. *Antimicrobial Drug Resistance*. Springer, Cham, pp: 265-268.
- Grayson L (2017) The use of antibiotics, a clinical review of antibacterial, antifungal, antiparasitic and antiviral drugs.
- Stahlmann R. (2002) Clinical toxicological aspects of fluoroquinolones. *Toxicol Lett* 127: 269-277.
- Scoper SV (2008) Review of third-and fourth-generation fluoroquinolones in ophthalmology: In-vitro and in-vivo efficacy. *Adv Ther* 25: 979-994.
- Sousa J, Alves G, Fortuna A, Falcão A (2014) Third and fourth generation fluoroquinolone antibacterials: A systematic review of safety and toxicity profiles. *Curr Drug Safety* 9: 89-105.
- Sykes JE, Blondeau JM (2014) Pradofloxacin: A novel veterinary fluoroquinolone for treatment of bacterial infections in cats. *Vet J* 201: 207-214.
- Winter RW, Kelly JX, Smilkstein MJ, Dodean R, Hinrichs D, et al. (2008) Antimalarial quinolones: Synthesis, potency and mechanistic studies. *Exp Parasitol* 118: 487-497.
- Emami S, Shafiee A, Foroumadi A (2010) Quinolones: Recent structural and Clinical developments. *IJPR* 4: 123-136.
- Monique IA, Alasdair PM (2003) Development of the quinolones. *J Antimicrob Chemother* 51: 1-11.
- Hubicka U, Żuromska-Witek B, Żmudzki P, Maślanka A, Kwapińska N (2013) Determination of sparfloxacin and its photodegradation products by thin-layer chromatography with densitometry detection. Kinetic evaluation of the degradation process and identification of photoproduct by mass spectrometry. *Anal Methods* 5: 6734-6740.
- Mitscher LA, Ma Z (2003) Fluoroquinolone antibiotics. Birkhäuser Basel, pp: 11-48.
- Peterson LR. (2001) Quinolone molecular structure-activity relationships: What we have learned about improving antimicrobial activity. *Clin Infect Dis* 33: S180-S186.
- Hayashi N, Nakata Y, Yazaki A (2004) New findings on the structure-phototoxicity relationship and photostability of fluoroquinolones with various substituents at position 1. *Antimicrob Agents Chemother* 48: 799-803.

25. Domagala JM (1994) Structure-activity and structure-side-effect relationships for the quinolone antibacterials. *J Antimicrob Chemother* 33: 685-706.
26. Oppegard LM, Streck KR, Rosen JD, Schwanz HA, Drlica K, et al. (2010) Comparison of in vitro activities of fluoroquinolone-like 2, 4-and 1, 3-diones. *Antimicrob Agents Chemother* 54: 3011-3014.
27. De Guidi G, Bracchitta G, Catalfo A (2011) Photosensitization reactions of fluoroquinolones and their biological consequences. *Photochem Photobiol* 87: 1214-1229.
28. Viola G, Facciolo L, Canton M, Vedaldi D, Dall'Acqua F, et al. (2004) Photophysical and phototoxic properties of the antibacterial fluoroquinolones levofloxacin and moxifloxacin. *Chem Biodivers* 1: 782-801.
29. Ouedraogo G, Morliere P, Bazin M, Santus R, Kratzer B, et al. (1999) Lysosomes are sites of fluoroquinolone photosensitization in human skin fibroblasts: A microspectrofluorometric approach. *Photochem Photobiol* 70: 123-129.
30. Koker EB, Bilski PJ, Motten AG, Zhao B, Chignell CF, et al. (2010) Real-time visualization of photochemically induced fluorescence of 8-halogenated quinolones: Lomefloxacin, Clinafloxacin and Bay3118 in Live Human HaCaT Keratinocytes. *Photochem Photobiol* 86: 792-797.
31. Zhao L, Dong YH, Wang H, et al. (2010) Residues of veterinary antibiotics in manures from feedlot livestock in eight provinces of China. *Sci Total Environ* 408: 1069-1075.
32. Bursch W (2001) The autophagosomal-lysosomal compartment in programmed cell death. *Cell Death Differ* 8: 569.
33. Sayama K, Kobayashi Y, Fujita H, Ito A, Tokura Y, et al. (2005) Determination of action spectrum for sparfloxacin-photosensitized single-strand breaks in plasmid pBR322 DNA. *Photodermatol Photoimmunol Photomed* 21: 287-292.
34. Turrens JF (2003) Mitochondrial formation of reactive oxygen species. *J Physiol* 552: 335-344.
35. Boya P, Andreau K, Poncet D, Zamzami N, Perfettini JL, et al. (2003) Lysosomal membrane permeabilization induces cell death in a mitochondrion-dependent fashion. *J Exp Med* 197: 1323-1334.
36. Singh J, Dwivedi A, Ray L, Chopra D, Dubey D, et al. (2018) PLGA nanoformulation of sparfloxacin enhanced antibacterial activity with photoprotective potential under ambient UV-R exposure. *Int J Pharm* 541: 173-187.