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UNAVAILING CLINICAL POTENTIAL OF GATIFLOXACIN, A PROMISING FLUOROQUINOLONE REVIEW

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ABSTRACT

Gatifloxacin is 8-methoxy fluoroquinolone introduced by Bristol-Myers Squibb in 1999. In May 2006, gatifloxacin was withdrawn by Bristol-Myers Squibb from the market because of it's severe dysglycemic events. As well as by notification of Union Health and Family Welfare Ministry of India on 18 March 2011 banned the manufacture, sale as well as distribution of gatifloxacin containing oral and injectable formulations from market. Certain in vitro experiments & post marketing surveillance devoted that dysglycemia viz. hypoglycemia, hyperglycemia is more common with gatifloxacin. In today's COVID 19 pandemic situation, gatifloxacin can act as antiviral through RNA messenger inhibitor or inhibition of viral helicases, topoisomerases II at low concentration. The fluoroquinolones like gatifloxacin, ciprofloxacin, ofloxacin, levofloxacin were found to be clinically effective in the treatment of the single-stranded RNA HCV and the non-enveloped, encapsulated DNA polyomavirus BK. So, gatifloxacin can be used to combact against corona virus. Therefore, observed potential severity of the reaction and increasing use of gatifloxacin, it is important to be aware with this phenomenon.

KEYWORDS: Gatifloxacin, Antibacterial, Dysglycemia, Antiviral, COVID 19.

INTRODUCTION

In 1999 Bristol-Myers Squibb introduced gatifloxacin, licensed the medication from Kyorin pharmaceutical company of Japan under the proprietary name Tequin for the treatment of respiratory tract infections, urinary tract infection, sexually transmitted diseases.[1,2] Gatifloxacin was marketed under the brand names like Gatiflo, Tequin and Zymar, which is an antibiotic of the fourth-generation fluoroquinolone family. In many countries, gatifloxacin is also available in different formulations like tablets, ophthalmic solution and aqueous solutions for intravenous therapy.[3,4] Gatifloxacin was originally developed at Kyorin and it was first licensed to Gruenenthal in Europe, and that company retains the rights to the product's oral and injectable formulations. Kyorin licensed gatifloxacin to BMS in October 1996, granting the pharmaceutical company development and marketing rights in the U.S., Canada, Australia, Mexico, Brazil and some other countries.[5,6]

Sumitomo Dainippon pharma agreed in April 2000 to comarket the oral Japanese formulation. Allergan was licensed Kyorin gatifloxacin in August of that year, gaining the drug's development and marketing rights in all territories except Japan, Korea, China and Taiwan. In June 2004, Lupin Pharmaceuticals in India signed an agreement with Allergan to promote the ophthalmic solution.[7,8]

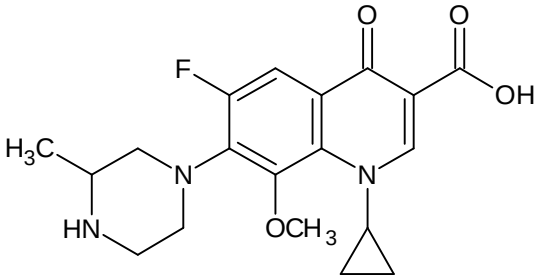


Figure 1: Structure of gatifloxacin.

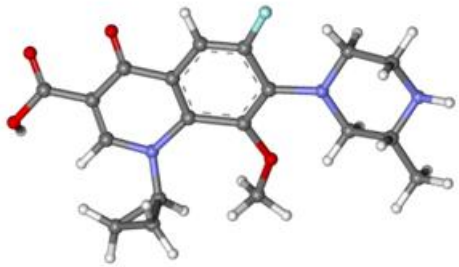


Figure 2: Ball and stick model of gatifloxacin.

Gatifloxacin is indeed a synthetically derived, novel antimicrobial fluoroquinolone agent used to treat a variety ofinfections. It has broad-spectrum of activity against gram positive, gram-negative, anaerobic and atypical microorganisms.[9,10] Gatifloxacin is a fourth generation fluroquinolone antibiotic. It is chemically known as 1 - cyclopropyl- 6 – fluoro 8 – methoxy – 7 - (3-methyl piperazin-1yl) - 4 - oxo - 1, 4- dihydro - quinoline-3-carboxylic acid shown in (Fig. 1). It is a crystalline powder and white to pale yellow in colour. Solubility of gatifloxacin is pH dependent, with maximum aqueous solubility (40-60 mg/ml) having pH range of 2-5, Methanol, Chloroform, DMSO. [11,12] The ball & stick model of gatifloxacin is also represented in (Fig. 2).

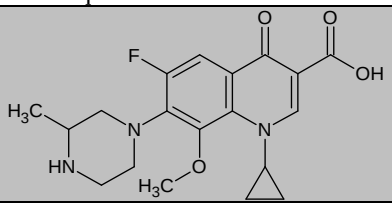
Mechanism of action

The possible mechanism of action of gatifloxacin is inhibition of topoisomerase II, topoisomerase IV, bacterial gyrase, which are involved in DNA (Deoxyribonucleic acid) replication, recombination and repair.[13-15] By interfering with gyrase, gatifloxacin can arrest bacterial cell growth[16,18] The affinity of quinolones with metal ion seems likely to be an important prerequisite of antibacterial action. Thus, gatifloxacin binding through a magnesium ion to the DNA-gyrase-complex takes place.[19-22]

Actually, broad range of anti-infective, antiviral, antiparasitic activities are due to one common mode of action, i.e., the inhibition of type II topoisomerases or inhibition of viral helicases. Thus to maintain the selective toxicity of fluoroquinolones, it can inhibit microbial topoisomerase at low concentrations but mammalian topoisomerase at much higher concentrations. Therefore, collected evidences suggested that standard doses of the fluoroquinolones are clinically effective against viral and parasitic infections, whereas higher doses were topically active against *Candida* species causing ophthalmological infections[23]

DRUG PROFILE[24-41]

Table 1: Drug profile.

Sr. No.	Gatifloxacin	
1.	Name of Compound	Gatifloxacin
2.	Class	Fluoroquinolone
3.	Structure	
4.	IUPAC Name	1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4oxo-3-quinolinecarboxylic acid sesquihydrate
5.	Molecular formula	$C_{19}H_{22}FN_3O_4$
6.	Molecular weight	375.4
7.	Nature	Solid
8.	Solubility	40-60 mg/ml at pH 2-5
9.	Dosage forms	Solid – Tablet Liquid – Opthalmic solution
10.	Brand nameTablet Opthalmic solution	Tequin - 200 mg, 400 mg Zymer, Zymaxid- 0.5%
11.	Therapeutic activity Tablet dosage forms Opthalmic solutions	Anthrax Prophylaxis, Bladder Infection, Bronchitis, Gonococcal Infection, UncomplicatedKidney Infections Otitis Media, Pneumonia, Sinusitis, Skin or Soft Tissue Infection, Active Tuberculosis, Urinary Tract Infection, Conjunctivitis, Conjunctivitis, BacterialOphthalmic Surgery
12.	Pharmacokinetic	Well absorbed fromthe gastrointestinal tractafter oral administrationwithabsolutebioavailabilityis 96% Gatifloxacinundergoeslimitedbiotransformation in humanswithlessthan 1% of thedoseexcreted in theurine as ethylenediamine&methylethylenediaminemetabolites
13.	Bioavailability	96%
14.	Melting point	182-185ºC
15.	Hydrogen bond donor	2
16.	Hydrogen bond acceptor	8
17.	Protein binding	20%
18.	Biological half life	7-14 hours

19.	Mechanism of Action	Inhibition of theenzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are requiredforbacterial DNA replication, transcription, repair, and recombination.
20.	Target	DNA gyrasesubunit A
21.	Cellular location	Cytoplasm, membrane, extracellular fluid
22.	Adverse drug reaction	Purpura, hypoglycemia, hyperglycemia
23.	Drug interaction	Dalfampridine, amoxicillin, clavulanate, celecoxib, Co-trimoxazole, sulfamethoxazole, trimethoprim, meperidine, dexamethasone

Structure activity relationship

Some derivatives of gatifloxacin are the combination of second aromatic or heteroaromatic ring with chemical scaffolds which is structurally characterized by various methods.[42-44] The side chain is attached to the 1st position of nitrogen significantly affects the potency of the drug.[45-47] The carboxylic moiety at position 3 is believed to be the portion of pharmacophore that binds to the DNA gyrase of the bacterial cell and thus it is important for antibacterial activity which does not interfere with the stereochemistry around this area.[48-49] The carbonyl and carboxylate groups of gatifloxacin bind with DNA by hydrogen bonding. Also, substitution of the bulky group at 5th position which is affects on biological activity.[50]

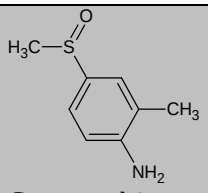
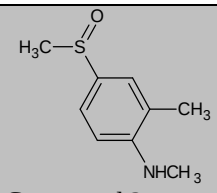
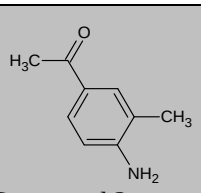
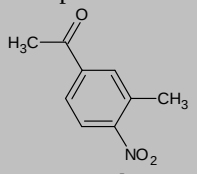
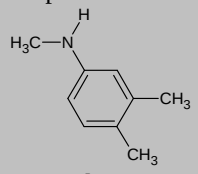
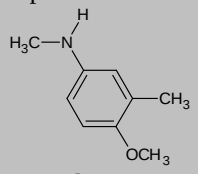
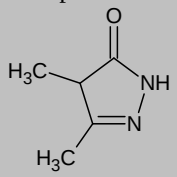
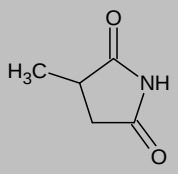
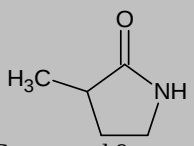
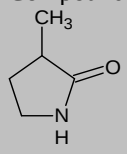
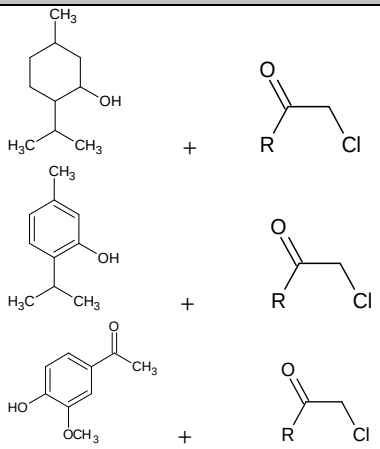
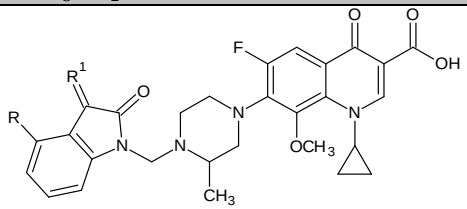
Fluorine atom at 6th carbon is responsible for phototoxicity.[51,52] The potency can be change where modification at 7th carbon of fluoroquinolone. The 8th methoxy group confers the good anaerobic activity. Fluoroquinolones bind with DNA in a stacking arrangement in such ways that aromatic ring is coplanar and the bonding interaction takes place between the substituents at the first position.[53,54] The resulting complex is stable and thus the activity of fluoroquinolones arises. The chemical modifications are hereby done to improve the activity and pharmacology of these drugs which are mainly focused over the stacking domain, the binding sites to the enzyme and DNA.[55,56]

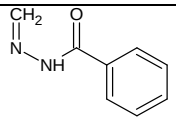
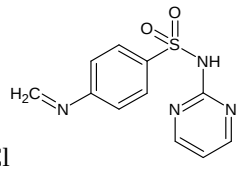
SYNTHETIC DERIVATIVES OF GATIFLOXACIN

According to literature survey, gatifloxacin derivatives were synthesized by using various chemical segments at 3rd, 4th, 7th, 8th position & reported the respective pharmacological action shown in (Table 2).

Table 2: Synthetic derivatives of gatifloxacin.

Sr. No.	Position	Derivatives			Biological activity
1.	**7th**	CN $COOCH_3$ $COOC_2H_5$ $COCH_3$	$(CN)_2$ $(COOCH_3)_2$ $(COOC_2H_5)_2$ $(COCH_3)_2$		**Antibacterial activity & Cytotoxicity[57,58]**
2.	**3rd.4th. 8th**	**3rd**	**4th**	**8th**	**Antibacterial activity & Antitubercular activity [59,60]**
		$CH_2OC(O)NEt_2$	H	H	
		CH_3	H	OCH_3	
		$CH_2OC(O)NHBu$	H	H	
		CH_3	H	OCH_3	
		$COOH$	H	H	
		CH_3	H	OCH_3	
		$COOH$	H	H	
		CH_3	H	OCH_3	
		CH_3	C_2H_5	H	
		CH_3	C_2H_5	OCH_3	

3.	**7th**	 Compound 1  Compound 2  Compound 3  Compound 4  Compound 5  Compound 6  Compound 7  Compound 8  Compound 9  Compound 10	**Antibacterial activity & Antifungal activity** **[61,62]**
4.	**3rd**		**Antibacterial activity** **[63,64]**
5.	**3rd**	$TbCl_3.6H_2O$	**Bacteriostatic activity** **[65,66]**
6.	**7th**	 **R** **R^1** F = $NNHCONH_2$ CH_3 = $NNHCONH_2$ Cl = $NNHCONH_2$ H = $NNHCONH_2$ F = $NNHCSNH_2$ CH_3 = $NNHCSNH_2$ Cl = $NNHCSNH_2$ H = $NNHCSNH_2$	**Antitubercular activity** **[67,68]**

		 F CH_3 Same as above Cl Same as above H Same as above  Cl F Same as above H Same as above CH_3 Same as above	
7.	**3rd**	**3-Carboxamide derivative** $C_6H_4.CH_3$ $C_{10}H_8$ C_6H_5 $C_6H_4NH_2$ $CO(NH)_2$ C_6H_4COOH COC_6H_5 $=C=SCH_3$ $C_{12}H_8$ **3-Carbohydrazide derivative** $=NH_2$ NHC_6H_5 **3-Carboxylate derivative** C_6H_5 $C_6H_4NH_2$ C_6H_4OH $C_6H_3(OH)_2$ C_6H_4OH	**Immunomodulatory effects & Chemiluminescence activity T - cell proliferation assay** [69-71]

WHY GATIFLOXACIN WAS BANNED IN INDIA?

Several clinical trials reported that, gatifloxacin is a safe drug. Gatifloxacin has the once daily dose, which shows lesser drug interactions than other fluoroquinolones and shows better pharmacokinetics, tolerability profile.[72-74] It is considered as an ideal quinolone in the management of various infectious diseases. Purpura, hypoglycemia, hyperglycemia are adverse drug reactions of gatifloxacin.[75-79]

Gatifloxacin having a tablet, 0.5% ophthalmic solution, intravenous dosage forms which sold under the brand names Gatiflo, Tequin and Zymar.[80-82] The gatifloxacin is from fourth generation of fluoroquinolone family having strong antibacterial activity.[83-85] By notification of Union Health and Family Welfare Ministry of India on 18 March 2011 banned the manufacture, sale as well as distribution of gatifloxacin containing oral and injectable formulations from the market. Because it bears high risk of serious dysglycemia such as hypoglycemia, hyperglycemia.[86-88]

But according to the prescribing information, similar thought was not extended to the gatifloxacin containing ophthalmic formulation.[89-91] The Drugs Controller General of India has announced that the topical formulations of gatifloxacin containing ophthalmic formulations like eye drops, eye ointments was not banned in the India.[92] Gatifloxacin is also available as tablets in many countries, and in various aqueous intravenous therapy solutions.[93] Systemically, in oral administration –the concentration of 400 mg gatifloxacin is 800 times higher than that of the concertration of 0.5 % gatifloxacin ophthalmic solution. By considering, 0.3% & 0.5% gatifloxacin ophthalmic solution causes very low systemic exposures. So gatifloxacin ophthalmic solution is systemically safer than gatifloxacin tablet [94,95]

Therefore, the systemic exposures resulting from gatifloxacin ophthalmic solution are not likely to pose any risk for systemic toxicities.[96-99] The relatively high numbers and rates of gatifloxacin-associated dysglycemia events were observed in clinical trials, cohort studies, case control studies, post marketing surveillance and case reports. While in case of oral formulation of gatifloxacin, hypoglycemia occurred in first two days and hyperglycemia on 3-6 days after administration of gatifloxacin. The onset of hyperglycemia occurs from 3 to 10 days after initiation of treatment but it can be resolved after discontinuation of gatifloxacin therapy within 24 hours.[100-102]

The monitoring program reveals that, increased risk of dysglycemia and showed that patients (diabetic and non-diabetic) receiving gatifloxacin had approximately 17 times the odds of having the hyperglycemia episode and 4 times the odds of having hypoglycemic episode compared to other antibiotics. Thus, certain post-marketing survey devoted that dysglycemic effects were observed not only in healthy volunteers but also in diabetic patients. Thus, thrust of the present scenario is to

resolve dysglycemic effect of gatifloxacin by structural modification in gatifloxacin[103-105]

Actually, the Diabetes mellitus commonly known as diabetes, is collectively caused by high blood sugar level. Diabetes mellitus is recognized as the fourth most commonly diagnosed chronic condition after hypertension, arthritis and dyslipidemia. Apart from age, the multiple risk factors like family history of diabetes, side effects of drugs like fluoroquinolones, obesity, hypertension are also significantly associated with diabetes.[106-108] Thus, according to literature review possible mechanism is that, gatifloxacin stimulate insulin release by blocking the ATP – sensitive K^+ channels of pancreatic cells cause acute hypoglycemia.However, the continuous treatment of gatifloxacin results in decreased islet insulin biosynthesis due to stimulating ATP – sensitive K^+ channels of pancreatic cells. It leads to reduced insulin level and, chronic hyperglycemia will occur.[109-112]

Additionally recent study suggested that, gatifloxacin affect gluconeogenesis by inhibiting pyruvate transport to mitochondria leads to hypoglycemia. In contrast, chronic hyperglycemic effect could be due to the down regulation of glucose transporter 1 expression in presence of gatifloxacin.[113-116]

The Gatifloxacin affects gluconeogenesis by inhibiting pyruvate transport to mitochondria in animal studies. Gatifloxacin has been shown to increase epinephrine release when given in higher doses, thus increasing the metabolic rate leading to hypoglycemic condition. In contrast, chronic hyperglycemic effect could be due to the down regulation of glucose transporter 1 (GLUIT) expression in presence of gatifloxacin. Interestingly, in the same study it was observed that, the gatifloxacin increases the glucose transporter promoter activity and decreases the mRNA (ribonucleic acid) level of the gene. Gatifloxacin affect the glucose metabolism due to altered protein expression.[117-119]

FUTURE PROSPECTIVE

The fluoroquinolones like Ciprofloxacin, ofloxacin, levofloxacin, and gatifloxacin were found to be clinically effective in the treatment of the single-stranded RNA HCV (HepatitisC Virus) and the non-enveloped, encapsulated DNA polyomavirus BK. Therefore, to control today's COVID 19 pandemic situation, gatifloxacin can be used to combact against corona virus as an antiviral.[23]

In 2020, World Health Organization announced worldwide pandemic resulting from the new virus is COVID-19. By early March 2020, the novel corona virus now named SARS-CoV-2 (Sever acute respiratory syndrome-coronavirus - 2) had infected worldwide.[120] Corona viruses are capable of adapting to new environments through mutation and recombination with relative ease and hence they are easily undergo to tissue tropism efficiently. Corona viruses are large, enveloped, positive standard RNA viruses. They have the largest genome among all RNA viruses; typically, it is ranging from 27 – 32 kb. The genome is packed inside a helical capsid formed by the nucleocapsid protein (N) further surrounded by an envelope.[121]

Actually, viral envelop is composed of 3 types of protein structural protein, membrane protein, envelop protein are involved in virus assembly. Inspite the spike protein (S) mediates virus entry into host cell. Some corona virus also encode &an envelop associated with hemagglutinin – esterase protein. Among these, structural proteins have spike forms large protrusions from the virus surface, giving corona virus the appearance of having crowns.[122] In addition to mediating virus entry, the spike is a critical determinant of viral host range & tissue tropism.[123]

CONCLUSION

All antibacterial agents have minimum risk and used only for appropriate indication. The literature survey suggested that, national cohort study showed the risk of hypo and hyperglycemia was greater with gatifloxacin. As the cases involving of gatifloxacin suggest, a drug found to be "safe" in clinical trials with younger, adults volunteers but in case of elderly or ill patients, might have very significant deleterious medical effects. During the post-marketing period, manufacturer should include the revision of warnings of serious disturbances regarding glucose metabolism. More research is needed on additional factors of gatifloxacin that may increase risk of hypo & hyperglycemia. Therefore, this knowledge is lead to focus on development of novel conjugated compounds of gatifloxacin will overcome risk of dysglycemia than single gatifloxacin drug which will reduce mortality rate & increase the quality of life.

In nutshell, based on one common mode of action, fluoroquinolones being commercially available as antibacterial agents are active against viruses, fungi, and parasites too, so this class of agents is probably representative of broad-spectrum anti-infectives in its true sense.

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