

## A systematic review of the quinolones, the novel pharmacotherapeutics, and the broad spectrum of their clinical indications and pharmacotherapeutic characteristics

Moumita Hazra<sup>1\*</sup>, Moumita Hazra<sup>2</sup>, Moumita Hazra<sup>3</sup>, Moumita Hazra<sup>4</sup>, Moumita Hazra<sup>5</sup>,  
Moumita Hazra<sup>6</sup>, Moumita Hazra<sup>7</sup>

<sup>1</sup>Medical Director, Medical Superintendent, Chief Executive Officer, Hospital Administrator, Head of Hospital Operations Management, Laboratory Director, Academic and Educational Centres Director, Medical Academics and Clinical Research Director, Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's Academic Centre, Dr. Moumita Hazra's Educational Centre, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, West Bengal, India

<sup>2</sup>Associate Professor, Head of Department In Charge, Department of Pharmacology, Mamata Medical College and Hospitals, Telangana, India

<sup>3</sup>Guest Professor, Head of Department, Department of Pharmacology, Hi-Tech College of Nursing, Odisha, India

<sup>4</sup>Former Associate Professor and Head of the Department In Charge, Department of Pharmacology, Rama Medical College Hospital and Research Centre, Rama University, Uttar Pradesh, India

<sup>5</sup>Former Assistant Professor and Former Head of the Department In Charge, Department of Pharmacology, Former Deputy Medical Superintendent, Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, Gouri Devi Institute of Medical Sciences and Hospital, West Bengal, K. D. Medical College Hospital and Research Centre, Uttar Pradesh, Hi-Tech Medical College and Hospital, Odisha, India

<sup>6</sup>Former Tutor and Former Junior Resident, Departments of Pharmacology, Pathology and Medicine, J. J. M. Medical College and Bapuji Hospital, Chigateri General Hospital, Dr. B. R. Ambedkar Medical College and Hospital, K. C. General Hospital, Karnataka, India

<sup>7</sup>Former Assistant Medical Director, Former Medical Editor, Former Clinical Trials Manager, GIOSTAR Institute of Regenerative Medicine Institutes, Hospitals and Laboratories, India

Received: 29-11-2021 / Revised: 16-12-2021 / Accepted: 01-01-2022

### Abstract

**Introduction:** The newer fluoroquinolones have broad-spectrum bactericidal activity, excellent oral bioavailability, good tissue penetration and favourable safety and tolerability profiles. **Objectives:** The objective of this systematic review was a prismatic illumination on the quinolones, with an emphasis on the newer quinolones, the novel pharmacotherapeutics, thus enlightening on the expansive spectrum of their clinical indications and pharmacotherapeutic characteristics. **Methods:** The study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration in June, 2016. At first, the steps of identification included the records which were identified through database searching and the additional records which were identified through other sources. This led to the steps of screening, which included the screened records after the duplicates were removed. From these screened records, few records were excluded, as per the exclusion criteria. Then, in the eligibility step, the full text articles were assessed for eligibility, from which few full text articles were excluded, according to the exclusion criteria, with adequate reasons. This led to the final inclusion step, where the studies were included in the qualitative synthesis of a systematic review, according to the inclusion criteria, and ultimately the studies were included in the quantitative synthesis. **Results:** This systematic review, performed in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration, June, 2016, contributed 2210 refined and relevant medical records, among total 3266 records obtained from the study databases search. It also describes the broad spectrum of their clinical indications and pharmacotherapeutic characteristics, which authenticate, validate, clarify, elaborate and complete this systematic review. **Conclusions:** To conclude, this systematic review provided the refined qualitatively synthesised medical records, study literature and databases on quinolones, and specifically on newer quinolones, with well-comprehensible elaborations.

**Keywords:** Systematic review, quinolones, newer quinolones, clinical indications, pharmacotherapeutic characteristics.

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### Introduction

With the advent of quinolones, and later the fluorinated 4-quinolones,

\*Correspondence

Dr. Moumita Hazra

Polyclinic and Diagnostic Centre, Hazra Nursing Home, Hazra Building, Jagadishpur Road, P.O. Domjur, Dist. Howrah, Kolkata, West Bengal, India

E-mail: [drmoumitahazra.june198017@gmail.com](mailto:drmoumitahazra.june198017@gmail.com)

the fluoroquinolones, the medical world has certainly taken long strides in treating enormous number of maladies. The newer fluoroquinolones have broad-spectrum bactericidal activity, excellent oral bioavailability, good tissue penetration and favourable safety and tolerability profiles[1-14].

This systematic review was conducted for revisiting and delving deep into the expansive spectrum of the clinical indications and uses of the quinolones, with an emphasis on the newer quinolones, as well as

their elaborate pharmacotherapeutic characteristics, and describing this vast spectrum with thorough explanations and analysis of the study literature and evidence compiled from the innumerable studies conducted, thus validating the growing necessities and efficacy of the newer quinolones, and emphasising their significance, as drugs, essential for multi-dimensional treatment of a wider range of mixed and complicated diseases, disorders and disabilities.

### Objectives

The objective of this systematic review was a prismatic illumination on the newer quinolones, with an emphasis on the newer quinolones, the novel pharmacotherapeutics, thus enlightening on the expansive spectrum of their clinical indications and pharmacotherapeutic characteristics.

### Methods

The study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration in June, 2016. At first, the steps of identification included the records which were identified through database searching and the additional records which were identified through other sources. This led to the steps of screening, which included the screened records after the duplicates were removed. From these screened records, few records were excluded, as per the exclusion criteria. Then, in the eligibility step, the full text articles were assessed for eligibility, from which few full text articles were excluded, according to the exclusion criteria, with adequate reasons. This led to the final inclusion step, where the studies were included in the qualitative synthesis of a systematic review, according to the inclusion criteria, and ultimately the studies were included in the quantitative synthesis.

#### i. Global Regulatory and Ethical Guidelines, in accordance with

The study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration, June, 2016, along with the ethical principles of the Declaration of Helsinki and Good Clinical Practices contained within the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH-E6), and in compliance with the global regulatory requirements[15-16].

This study involved almost negligible risk, of any type, to the patients. This study design provided an equal opportunity to all the eligible patients to be included in the study. The patients who were included in the study were kept confidential.

#### ii. Database, medical evidence and review literature search methodology

In this Systematic Review study, any or all types of original research studies, systematic reviews, meta-analyses, case reports, case series, narrative reviews, study series, parallel studies and similar kind of studies or reviews, which were either qualitative, or quantitative, or both qualitative as well as quantitative, in their description of the investigative newer quinolones, were included. Published medical articles and archival literature, obtained from various global electronic medical search engines and databases like Google Scholar, EMBASE, MEDLINE, Cochrane Library, PubMed, review of proceedings from selected scientific meetings, medical conferences, medical congress, medical summits, clinical trial registries, bibliographies of retrieved citations and reference lists, and expert recommendations, were searched manually, without a language or regional restriction. The comprehensive search was initiated with the titular keywords search, a search using an exploded medical subject headings (MeSH) and textword search, along with the numbered year text search. The recent advances articles on the newer investigative quinolones were searched within the recent publication time-period of mid-2015 to 2022, to derive the current investigative research database, medical evidence and review literature.

#### iii. Published articles filtration process, along with determination of methodological quality

In this systematic review, the searched published full text articles, including the abstracts and titles, and medical conference, medical congress, medical summits and scientific meeting abstracts, were collected, thoroughly screened and verified, at first. Duplicate articles were removed. The titles and abstracts of identified citations were appraised, after the duplicates were removed. Bibliographies of identified articles were subsequently reviewed for additional citations. Then, it was assessed to determine if they fulfilled the following study selection criteria, that is the inclusion and the exclusion criteria. Following this, the full text was obtained for the remaining studies, the substantiation of the data derived was validated and compared to the pre-established inclusion criteria, before final inclusion in the review.

The study selection criteria were the following

##### (a) The inclusion criteria were

- The published articles on the newer investigative quinolones, which were based on their expansive and ever-progressive spectrum of clinical indications and uses and which enlighten on their improved anti-microbial spectrum, pharmacokinetic and pharmacodynamic properties, efficacy and safety profiles and pharmacotherapeutic characteristics and qualities, appropriate for their relevance in the multi-dimensional treatment of a wider range of mixed, refractory and complicated diseases, disorders and disabilities.
- The original research studies, systematic reviews, meta-analyses, case reports, case series, narrative reviews, study series, parallel studies and similar kind of studies or reviews, of any or all types, which were either qualitative, or quantitative, or both qualitative as well as quantitative, in their description of the investigative newer quinolones, were included in this systematic review.
- The publication time-frame was chosen to be recent, that is, within a span of the past 5.5 years, emphasising on the well-maintained pharmacogenomic and epigenetic time-frames of evolution.
- Any or all types of observational, descriptive and analytical research studies were included.
- Global, uni-centre and multi-centre studies, belonging to heterogenous pharmacogenomic and epigenetic constitution, of the recent evolutionary time-frame, were included.
- Studies based on either children, adult, pregnant and lactating women, or old patients, or all types of patients, were included.
- Studies based on the treatment of any or all clinically indicated types of diseases were included.
- Studies conducted at any type of small, medium or large medical establishment set-up were included.
- Studies performed on any gender of patients were included.
- Studies performed on any age group of patients were included.
- Studies with any or all routes of drug administration of the newer quinolones were included.

##### (b) The exclusion criteria were

- The studies which described the procedures of formation, preparation of formulations and interactive handling of the quinolones were filtered, to maintain an already standardised time-bound qualification of the characteristics of the quinolones.
- *In vitro* studies were excluded, to enhance the degree of clinical relevance.
- Studies performed with zoological or botanical subjects were excluded, to enhance the clinical relevance and for appropriate clinical applicability.
- Studies performed on seriously ill patients were excluded.
- Studies performed on patients with co-morbidities or on any concomitant medication were excluded.
- Studies older than 7 years were excluded.

Each study was assessed for allocation concealment, blinding, reporting of losses to follow-up or missing outcome assessments,

evidence of important baseline differences between the groups, analysis on an intention-to-treat basis and use of a sample size calculation.

**i. Methodology of obtaining pertinent medical database, evidence, descriptive and analytical literature, after bias assessment**

After examining the quality of the full articles, the medical data and evidence were independently obtained by the principal investigator who was simultaneously the author, using a review protocol and a pre-structured data collection forms, containing different systematic review determinant criteria based on well-defined objectives, which were subsequently reviewed, to refine the medical database and evidence, after assessing and eliminating the study bias. The medical data and evidences extracted from the study resources were of heterogenous qualitative or quantitative nature, or both. Studies with any or all types of study characteristics and outcomes were obtained to derive the pertinent qualitative and quantitative descriptive and analytical literature, the main outcome measures being clinical indications and pharmacotherapeutic uses, chemical drug structure, mechanisms of action, pharmacological actions, pharmacokinetics, pharmacodynamics, medication adverse effects and comparative safety, pharmacotherapeutic efficacy, dosage details, drug interactions, drug contraindications, pharmacogenetic or pharmacogenomic details and newer investigative recent advances. The risk of bias of the studies were also assessed, which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias (i.e., design-specific risks of bias, baseline imbalance, blocked randomization in unblinded trials) with the Cochrane Risk of Bias tool and other tools of bias assessment. Methodological quality of the included studies were assessed after independently evaluating each of them in keeping with the Cochrane Collaboration's tool for assessing risk of bias. Using this method, each study was rated as having low, unclear or high risk of bias for domains including "selection bias", which is split into two sub-groups relating to the appropriateness of the randomisation procedure and allocation of participants to study groups. Presence of "performance bias" and "detection bias" relating to the blinding of participants, personnel and outcome assessment was also assessed, in addition to "attrition bias" and "reporting bias" which relate to incomplete outcome data and selective reporting. The domain "other bias" relates to any potential sources of bias which are not covered by the outcome categories, intervention and control groups, or bias arising from particular study designs.

**ii. Categorisation and detailing of the different determinant criteria for this systematic review**

The categorisation of the refined medical databases and evidences, from the published articles, was made on the basis of the following broad categorisations :

- (1) Systematic review : Assessments related to the study processes
- (2) Systematic review : Assessments related to the clinical indications of the newer quinolones
- (3) Systematic review : Assessments related to the pharmacotherapeutic characteristics

This systematic review was performed on the following detailed different determinant criteria under these broad categorisations :

- (1) **Systematic review : Assessments related to the study processes**, based on :

**A. Identification**

- i. Total published articles chosen,
- Total no. of records identified through database searching,
  - a. Total no. of additional records identified through other sources.

**B. Screening**

- i. No. of records after duplicates removed,
- ii. No. of records screened,
- iii. No. of records excluded

**C. Eligibility**

- (i) No. of full articles assessed for eligibility,
- (ii) No. of full articles excluded, with reasons,
- (i) Total number of articles found relevant to the broad categorisations,
- (ii) Total number of articles excluded, based on the exclusion criteria,
- (iii) Total number of articles included, based on the inclusion criteria

**D. Inclusion**

- (i) Total no. of articles, included in the systematic review

**E. Analysis**

**a) General Analytical Details :**

- (i) Total number of articles analysed for the systematic review,

**b) Advanced Analytical Details :**

- (i) Number of articles, based on their nature,
  - (a) qualitative,
  - (b) quantitative,
  - (c) both, qualitative and quantitative
- (ii) Number of articles, based on their types,
  - (a) original research article,
  - (b) review article,
  - (c) systematic review,
  - (d) meta-analysis,
  - (e) case report,
  - (f) case series,
  - (g) narrative review,
  - (h) study series,
  - (i) parallel study,
  - (j) mixed study type
- (iii) Number of articles, based on the different study designs,
- (iv) Assessment of principal accuracy measures, based on : Relative study content quality of the published articles, based on (1) the comprehensive degree of correlation of the articles to the determinant criteria of this systematic review, as well as (2) the methodological quality, determined by the total number of included determinant criteria in the studies and the methodological quality assessment, by the key indicators of trial methodological quality, like allocation concealment, blinding, placebo-controlled, analysis by intention-to-treat, baseline imbalance, pre-defined outcomes, loss to follow-up, sample size calculation, keeping in consideration with the Cochrane Collaboration's tools, and (3) the quality of the subjective details of the study literature content, determined by the specificity and the significance of the study literature content
  - (a) high quality,
  - (b) medium quality,
  - (c) low quality
- (v) Risk of bias assessment : Relative bias assessment of the studies in the published articles, determined by the total proportionate bias in the studies, including "selection bias", "performance bias", "detection bias", "attrition bias", "reporting bias", and "other bias", keeping in consideration the Cochrane Collaboration's tool and other tools for assessing risk of bias
  - (a) high bias,
  - (b) medium bias,
  - (c) low bias,
- (vi) Assessment of applicability : Relative significance of the published articles, determined by the proportionate degree of correlation to the objective of this systematic review
  - (a) high significance,
  - (b) medium significance,
  - (c) low significance

**(2) Systematic review : Assessments related to the clinical indications of the newer quinolones, based on :**

- (i) pharmacotherapeutic efficacy
  - (a) high
  - (b) medium

- (c) low  
(ii) pharmacotherapeutic safety  
(a) high  
(b) medium  
(c) low  
(iii) total duration of treatment required  
(iv) total duration of recovery  
(v) degree of recovery  
(a) high  
(b) medium  
(c) low  
(vi) degree of improvement in recovery confirmation tests and evaluations  
(a) high  
(b) medium  
(c) low  
(i) if any multiorgan involvement, after medication  
(ii) if any concomitant medication required, along with the newer quinolones  
(ix) if any supplementary treatment required, after medication for:
- single, multiple, multi-resistant, concurrent and recurrent infections:
    - bactericidal,
    - anti-viral,
    - anti-fungal,
    - anti-protozoal,
    - drug-resistant tuberculosis,
    - drug-resistant leprosy,
    - coronaviridae – 19,
    - mixed infections,
  - comedolytic or anti-comedogenic
  - anti-inflammatory
  - refractory inflammations
  - immunomodulatory
  - anti-neoplastic or anti-malignant
  - miscellaneous mixed, refractory and complicated diseases, disorders and disabilities

## F. Analysis

### b. Advanced Analytical Details

#### (3) Systematic review: Assessments related to the pharmacotherapeutic characteristics, based on

- chemical drug structure,
- mechanisms of action,
- pharmacological actions,
- pharmacokinetics,
- pharmacodynamics,
- medication adverse effects and comparative safety,
- comparative pharmacotherapeutic efficacy,
- dosage details,
- drug interactions,
- drug contraindications and suitability,
- pharmacogenetic or pharmacogenomic pharmacotherapeutic suitability,
- newer investigative recent advances.

#### (i) The process of refined data and evidence compilation:

The medical databases and evidences were thoroughly reviewed and the compilation of the data was done by selection and categorisation

of the published articles, based on the above-mentioned categorisations and the different detailed determinant criteria of the systematic review. Then, the study literature was further critically and systematically reviewed; and refined into a standardised, well-structured form of aggregated refined medical data and evidence compilation.

#### (ii) The process of data and evidence recording:

The refined medical data and evidence obtained were properly recorded manually in a pre-structured analytical proforma. The standardised, well-structured compilation of the study literature was subsequently undertaken for a final analysis.

#### (iii) The methodology of the final analysis of data and evidence of the systematic review:

The final standardised, well-structured compilation of the study literature was then successively synthesised into a sequentially analytical systematic review, based on the comprehensive integration of the compiled study literature. This comprehensive integration and synthesis of the compiled study literature was performed by combining the results of the different studies, and describing the integrated study literature, including the description of the variability between the different studies. This process included:

- managing the multiple features of the outcome measures,
- managing the multiple threshold ranges of the study results,
- managing the multiple index assessments, managing the different types of study results, including indeterminate results,
- categorisation and detailing of the extensive study literature, along with comparisons, and managing the different reference standards[15-24].

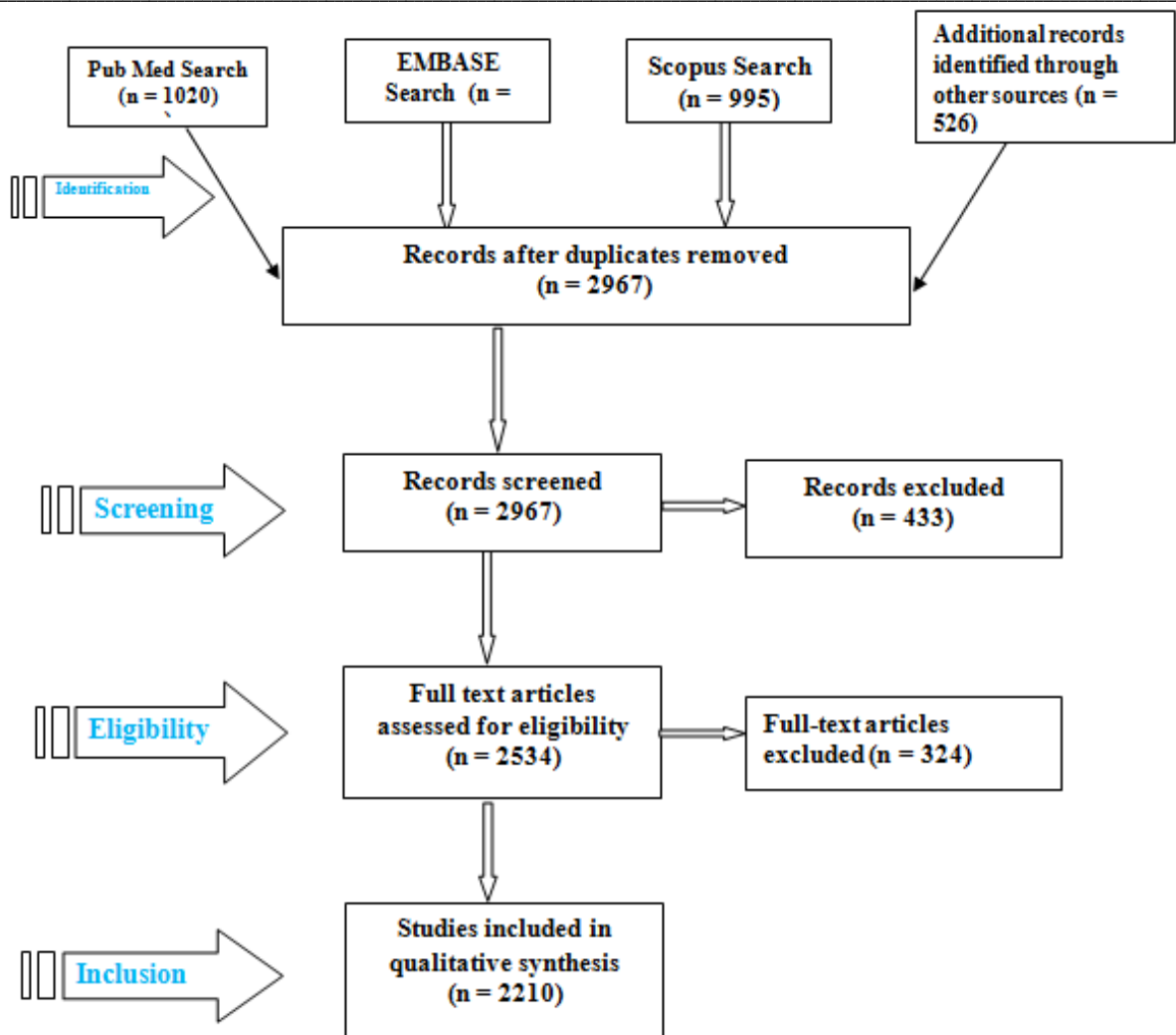
#### (i) Selective investigative and experimental elucidations on the newer quinolones, from the analytical compilation of pharmacotherapeutic databases and evidences:

Certain selective investigative and experimental elucidations were chosen for elaboration, from the comprehensive systematic review of the published articles, to corroborate this rational pharmacotherapeutic analytical review of the pharmacotherapeutic study literature, databases and evidences on the newer quinolones.

## Results

### (i) The results of this Systematic Review

In accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration, June, 2016, in identification stage, the study literature search on quinolones, and more specifically on the newer quinolones, contributed 1020 records in PubMed search, 725 records in EMBASE search, 995 records in Scopus search, and 526 records in additional databases search, identified through other sources. The records, after removing the duplicates, were 2967. In the screening stage, the records screened were 2967, with the exclusion of 433 records, according to the exclusion criteria. In the eligibility stage, the full text articles assessed for eligibility were 2534, with the exclusion of 324 full text articles, according to the exclusion criteria. In the final inclusion stage, the records ultimately included in the qualitative synthesis, according to the inclusion criteria, was 2210. These 2210 records were the refined contributions of this systematic review. Thus, this systematic review contributed 2210 refined and relevant medical records, among total 3266 records obtained from the study databases search, as depicted in Figure 1.



- (ii) The investigative and experimental elucidations on the quinolones, and more specifically the newer quinolones, from the analytical compilation of pharmacotherapeutic databases and evidences was also described, in complete details, to authenticate, validate, elaborate, clarify and complete the qualitative details of the conducted systematic review.

#### Discussion

In this study, in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration, June, 2016, in identification stage, the study literature search on quinolones, and more specifically on the newer quinolones, contributed 1020 records in PubMed search, 725 records in EMBASE search, 995 records in Scopus search, and 526 records in additional databases search, identified through other sources. The records, after removing the duplicates, were 2967. In the screening stage, the records screened were 2967, with the exclusion of 433 records, according to the exclusion criteria. In the eligibility stage, the full text articles assessed for eligibility were 2534, with the exclusion of 324 full text articles, according to the exclusion criteria. In the final inclusion stage, the records ultimately included in the qualitative synthesis, according to the inclusion criteria, was 2210. These 2210 records were the refined contributions of this systematic review.

The following selected qualitative investigative and experimental elucidations on the quinolones, and more specifically the newer quinolones were described:

**Delafloxacin**, a new fourth generation broad-spectrum anionic fluoroquinolone, has increased accumulation in bacteria allowing for enhanced bactericidal activity[25-41].

**Sitafloxacin**, a new oral fluoroquinolone, used for the treatment of Buruli ulcer[42-43].

**Sparfloxacin**, a highly potent third generation fluoroquinolone, and is 37-45% bound to plasma proteins, with high degree of extensive tissue penetration. It diffuses well into tissues and respiratory tract secretions and concentrates within macrophages, suitable for treating respiratory diseases[44].

**Zabofloxacin**, an investigational novel fluoronaphthyridone quinolone antibiotic, is implicated in the treatment of acute bacterial exacerbation of chronic obstructive pulmonary disease, multidrug-resistant infections due to gram-positive bacteria like *Streptococcus aureus*, *Streptococcus pyogenes* and *Streptococcus pneumoniae*, *Neisseria gonorrhoea* causing quinolone-susceptible (QSSP) and quinolone-resistant gonorrhoea (QRSP), community-acquired respiratory tract infections, caused by *Haemophilus influenzae* and *Moraxella catarrhalis*, COPD patients with moderate exacerbations, and community-acquired acute respiratory tract infections[45-47].

**Finafloxacin**, a broad-spectrum fluoroquinolone antibiotic, is used to treat *Pseudomonas aeruginosa* and *Staphylococcus aureus* causing

acute otitis externa, and possesses activity against both gram-positive and gram-negative bacteria, including *Helicobacter pylori*[48-50].

**Garenoxacin** is a newly developed novel des-fluoro (6) quinolone, which demonstrates wide spectrum of antibacterial activity against gram positive, gram negative, atypical and anaerobic pathogens. Its clinical indications are pharyngitis, sinusitis, laryngitis, tonsillitis, otitis media, acute bronchitis, pneumonia and secondary infection in chronic respiratory lesion[51-52].

**Ozenoxacin** is a topical novel non-fluorinated quinolone antibiotic, which was shown to be bactericidal against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*, methicillin-susceptible and methicillin-resistant *Staphylococcus epidermidis*, *Streptococcus pyogenes* and *Streptococcus agalactiae*[53-55].

**Aravofloxacin (JNJ-Q2)** is a novel fifth-generation broad-spectrum aminoethylidene piperidine fluoroquinolone that has excellent in vitro and in vivo activity against a variety of gram-positive and gram-negative organisms, being developed for the treatment of acute bacterial skin and skin-structure infections and community-acquired pneumonia and methicillin-resistant *Staphylococcus aureus* (MRSA) infections[56-58].

**Merafloxacin** is a fluoroquinolone antibacterial that inhibits the pseudoknot formation which is necessary for the frameshift in the SARS-CoV-2 genome. It is a potential drug for SARS-CoV-2[59-60].

**WQ-3810**, a newer fluoroquinolone, demonstrated the most potent activity against the multidrug-resistant pathogens. It has high potential for the treatment of *Mycobacterium tuberculosis*. It is a next generation respiratory fluoroquinolone. WQ-3810 is a candidate drug for the treatment of quinolone resistant *Salmonella Typhimurium* infection. The potential bactericidal effect of WQ-3810 on *Acinetobacter baumannii*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Neisseria gonorrhoeae*, *E. coli* and *Mycobacterium leprae* has been proved[61-62].

**Laseufloxacin** is a fluoroquinolone antibiotic drug for the treatment of community-acquired pneumonia, otorhinolaryngological infections, and respiratory tract infections, caused by gram-positive bacteria including *Streptococcus pneumoniae* and *Streptococcus anginosus*[63-66].

This systematic review provided the refined qualitatively synthesised medical records, study literature and databases on quinolones, and specifically on newer quinolones, with well-comprehensible elaborations.

### Conclusion

Therefore, this systematic review, performed in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration, June, 2016, contributed 2210 refined and relevant medical records, among total 3266 records obtained from the study databases search. It also describes the broad spectrum of their clinical indications and pharmacotherapeutic characteristics, which authenticate, validate, clarify, elaborate and complete this systematic review.

### Acknowledgements

My gratitude to the Departments of Pharmacology, Clinical Pharmacology, Molecular Pharmacology, Pharmacovigilance, Rational Pharmacotherapeutics, Clinical Pathology, Cytopathology, Pathology, Laboratory Medicine, Molecular Diagnostics, General Medicine, Molecular Medicine, Respiratory Medicine, Infertility and Reproductive Endocrinology, Neonatology, Medical Academics, Medical Education, Medical Administration, Medical Directorship, Medical Administrative Planning and Strategies, and Clinical Research, Dr. Moumita Hazra's Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's Academic Centre, Dr. Moumita Hazra's Educational Centre, Hazra Nursing Home, Hazra Polyclinic And Diagnostic Centre, Dr. Moumita Hazra's World Enterprises, Shri Ramkrishna Institute of Medical Sciences and Sanaka Hospitals, Gouri Devi Institute of Medical Sciences and Hospital, K. D. Medical College Hospital and Research Centre, Hi-Tech Medical College and

Hospital, Rama Medical College Hospital and Research Centre, Rama University, Mamata Medical College and Hospitals, J. J. M. Medical College and Bapuji Hospital, Chigateri General Hospital, Dr. B. R. Ambedkar Medical College and Hospital, K. C. General Hospital, GIOSTAR Institute of Regenerative Medicine Institutes, Hospitals and Laboratories, and, the global electronic medical search engines and databases like Google, Google Scholar, EMBASE, MEDLINE, Cochrane Library, PubMed, medical conferences, medical congress, medical summits, scientific meetings, and clinical trial registries, for the successful completion of this systematic review project.

### Declarations

#### Conflicts of interest

No conflicts of interest

#### Funding sources

No funding sources

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