The top 100 cited studies on bacterial persisters: A bibliometric analysis

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Background: Bacterial persisters are thought to be responsible for the recalcitrance and relapse of persistent infections, and they also lead to antibiotic treatment failure in clinics. In recent years, researches on bacterial persisters have attracted worldwide attention and the number of related publications is increasing. The purpose of this study was to better understand research trends on bacterial persisters by identifying and bibliometrics analyzing the top 100 cited publications in this field.

Methods: The Web of Science Core Collection was utilized to retrieve the highly cited publications on bacterial persisters, and these publications were cross-matched with Google Scholar and Scopus. The top 100 cited publications were identified after reviewing the full texts. The main information of each publication was extracted and analyzed using Excel, SPSS, and VOSviewer.

Results: The top 100 cited papers on bacterial persisters were published between 1997 and 2019. The citation frequency of each publication ranged from 147 to 1815 for the Web of Science Core Collection, 153 to 1883 for Scopus, and 207 to 2,986 for Google Scholar. Among the top 100 cited list, there were 64 original articles, 35 review articles, and 1 editorial material. These papers were published in 51 journals, and The Journal of Bacteriology was the most productive journal with 8 papers. A total of 14 countries made contributions to the top 100 cited publications, and 64 publications were from the United States. 15 institutions have published two or more papers and nearly 87% of them were from the United States. Kim Lewis from Northeastern University was the most influential author with 18 publications. Furthermore, keywords co-occurrence suggested that the main topics on bacterial persisters were mechanisms of persister formation or re-growth. Finally, "Microbiology" was the most frequent category in this field.

Conclusion: This study identified and analyzed the top 100 cited publications related to bacterial persisters. The results provided a general overview of bacterial persisters and might help researchers to better understand the classic studies, historical developments, and new findings in this field, thus providing ideas for further research.

KEYWORDS
bacterial persisters, bibliometric analysis, top-cited, citation analysis, VOSviewer
Introduction

Persistent bacterial infections pose significant public health problems, which increase the treatment time and costs, as well as cause death of millions of people every year (Monack et al., 2004; Chen and Wen, 2011; Martinez and Abel zur Wiesch, 2018). Persistent bacterial infections are related to recurrent and recalcitrant infectious diseases in clinics, like implant device-related infections, lung infections of cystic fibrosis patients, urinary tract infections, and tuberculous granulomas (Singh et al., 2000; Anderson et al., 2004; Mack et al., 2004; Monack et al., 2004; Fisher et al., 2017). There are great medical challenges in treating these chronic infectious diseases as they are hard to be eradicated by antibiotics. Both the host and bacterial factors are involved in the antibiotic treatment failure, including immunosuppression, immunosurveillance, antibiotic recalcitrance, and biofilms (Monack et al., 2004; Fisher et al., 2017). Besides, the presence of bacterial persisters has attracted more attention because of their important role in persistent infections (Zhang, 2014; Fisher et al., 2017). Bacterial persisters are a small fraction of non-growing bacteria that are tolerant to antibiotics, and have been shown to accelerate the emergence of antibiotic resistance and relate to the resistance of biofilms (Cohen et al., 2013; Levin-Reisman et al., 2017; Spoering and Lewis, 2001; den Bergh et al., 2017). Bacterial persisters were first observed by Gladys Hobby (Hobby et al., 1942). She found that a small number of bacteria could survive under intensive antibiotic treatments in the culture. Then, Joseph Bigger named this subpopulation “persisters” in 1944 (Bigger, 1944). Over the last few decades, researches on bacterial persisters have made significant progress. For example, several studies showed that epigenetic factors can promote the phenotypic switching between persisters and normal-state bacteria (Balaban et al., 2004; Dhar and McKinney, 2007; Helaine et al., 2014). However, a bibliometrics analysis on bacterial persisters that reflects these advances is still lacking.

The citation frequency of a publication usually reflects its’ academic impact and the level of interest of the research community in a particular field. Therefore, a high number of citations indicate the significant contributions of this paper in the field and the potential of the paper to trigger a new research direction (Van Noorden et al., 2014; Fardi et al., 2017). Analysis of the most cited publications, especially the top 100 cited publications, provides insight into the most significant achievements of past researches over the recent decades, and this information can then be used to guide future research (Godin, 2006; Arshad et al., 2020). Currently, numerous bibliometrics studies have been performed to determine the characteristics of the most cited publications in different fields, such as emergency medicine, psychiatry, medical informatics, immunology, orthodontics, and so on. (Tsai et al., 2006; Nadri et al., 2017; Tarazona et al., 2018; Jiang et al., 2019; Zhang et al., 2019; Zhang et al., 2021). Moreover, several studies have analyzed the top 100 cited publications in tuberculosis, pneumonia, and antibiotics (Zhang et al., 2017; Wang et al., 2019; Arshad et al., 2020). However, no bibliometrics analysis has been conducted to analyze the most cited publications in the field of bacterial persisters. Hence, this study aimed to identify the top 100 cited publications on bacterial persisters, and to provide a global perspective on the current status of bacterial persisters by analyzing the publication years, number of citations, characteristics of these papers, authors, countries, institutions, keywords and subject categories.

Materials and methods

Search strategy and inclusion criteria

Publications concerning bacterial persisters were searched from the Web of Science Core Collection (WosCC) database on 23 June 2022. The search strategy was as follows: TS (Topics) = (persist*$ OR "persistent bacteri*" OR “antibiotic persisten*” OR “antibiotic tolerance*”). No restrictions on country, publication year, and language were implemented on the investigation. The search results were sorted based on the citation frequency and two authors screened the full texts to identify the top 100 cited papers on bacterial persisters. The citation counts of these papers were cross-matched with Scopus and Google Scholar. Only publications focusing on bacterial persisters were included in the bibliometric analysis, while publications that mentioned persisters in passing were excluded. Disagreements were resolved by consensus-based discussion.

Data extraction

The following information of each publication was extracted from the WoS database: authors, title, journal, publication year, number of citations, country, institution, language, type of article, keywords, and subject categories. The impact factors (IFs) of the journals were manually supplemented from the Journal Citation Report (JCR) (Clarivate Analytics, Philadelphia, United States, available from https://jcr.clarivate.com/). For publications with two or more authors, the first-ranked author was identified as the first author, and the last-ranked author was identified as the last author. The counting of institution or country was based on the institution or country of the first author. For first authors with more than one institution or country, the first institution and country were used as country of origin. Similarly, the first category was selected for publication with more than one subject categories in the WoS database.
Statistical analysis

Statistical analyses of descriptive data were performed using Microsoft Excel 2010 and IBM SPSS Statistic 26.0. The Spearman rank test was utilized to analyze the correlation between variables among the age of publications, citation frequency, and IFs. The $p$ value < 0.05 was defined as statistically significant. The VOSviewer 1.6.17 (Leiden University, the Netherlands, available from https://www.vosviewer.com/) (van Eck and Waltman, 2010; van Eck and Waltman, 2017) was applied to map the co-occurrence network of keywords. Keywords, which appeared more than two times in the top 100 cited publications, were presented in the co-occurrence network. In the network, each circle represented a keyword and the size of the circle represented the occurrence time of the keyword. Circles in the same color represented that these keywords were included in the same cluster. The circles were connected if they appeared in the same publication and the thickness of the line represented the number of times they appeared together.

Results

Year of publications and citations analysis

The top 100 cited papers were published between 1997 by Domingue and Woody (1997) and 2019 by Pang et al. (2019) and Balaban et al. (2019), but no publication in 1998 was included (Figure 1). In addition, 2013 and 2014 were the most productive years with more than 10 publications. The total citations per year of these publications showed a continuous upward trend over time, with the highest citations of 4,180 in 2020 (Figure 1).

The Top 100 cited publications on bacterial persisters along with their total citations in WoSCC, Scopus, and Google Scholar were listed in Table 1. These publications received a total of 33,638 citations in WoSCC, 35,097 citations in Scopus, and 54,194 citations in Google Scholar. The citation frequency of each publication ranged from 147 to 1,815 (WoSCC), 153 to 1,883 (Scopus), and 207 to 2,986 (Google Scholar). There were only four publications that had citations more than 1,000 times in WoSCC and Scopus, but nine publications in Google Scholar. The most cited paper was published by Nathalie Q. Balaban et al. (2004) with citation frequency of 1815 (WoSCC), 1883 (Scopus), and 2,986 (Google Scholar), describing the phenotypic switch of bacterial persistence. Besides, the publication entitled “Antibiotic resistance in Pseudomonas aeruginosa: mechanisms and alternative therapeutic strategies” had the largest mean citations per year ($n = 141$ of WoSCC, $n = 147$ of Scopus, and $n = 241$ of Google Scholar), which was published by Zheng Pang et al. (2019) in Biotechnology Advances in 2019.

The Spearman rank test indicated that there was a statistically significant downward trend in the mean citations per year with the increase in publication age ($r = -0.488, p < 0.001$ of WoSCC; $r = -0.489, p < 0.001$ of Scopus; $r = -0.422, p < 0.005$ of Google Scholar) (Figure 2A, Supplementary Figures S1A, S1B). However, no significant relationship was observed between the age of publications and the number of total citations ($p = 0.248$ of WoSCC; $p = 0.209$ of Scopus; $p = 0.018$ of Google Scholar) (Figure 2B, Supplementary Figures S1C, S1D).

Characteristics of publications

The top 100 cited publications on bacterial persisters were all written in English. Among the publications, there were 64 original articles, 35 review articles, and one editorial material. The citation frequencies for each publication type were 20,287 (original articles), 13,183 (review articles), and 168 (editorial material). However, the type of review had the highest average citation count per paper ($n = 377$).

Overall, the top 100 cited papers on bacterial persisters were published in 51 journals (Table 2). The 2021 IFs of these journals ranged from 2.82 (FEMS Microbiology Letters) to 112.288 (Nature Reviews Drug Discovery), and 23 journals had 2021 IFs greater than 10. Journal of Bacteriology published the greatest number of papers (eight papers), followed by Nature Reviews Microbiology (seven papers) and Antimicrobial Agents and Chemotherapy (seven papers). In addition, Science had the highest total citations (3,678) with six publications. But, the highest average citation count per publication ($n = 844$) belonged to Nature Reviews Drug Discovery. The Spearman rank test indicated that the number of published papers ($p = 0.255$), total citations ($p = 0.300$), and average citation count per publication ($p = 0.439$) did not correlate to the 2021 IFs (Supplementary Figure S2).
Countries, institutions, and authors

A total of 14 countries contributed to the top 100 cited publications on bacterialpersisters (Table 3). The United States was the most productive country in this field with 64 publications. England ranked second with eight publications, followed by Israel (five publications), and Switzerland (three publications). Furthermore, the United States was also the most influential country on bacterial persisters with the highest total citations (23,129). New Zealand had the highest average citation count per publication (508).

Fifty-five institutions participated in the top 100 cited publications, therein, 15 institutions have published two or more papers (Table 4). Most of these institutions were from the United States (13 institutions, 87%), and only one institution each from Israel and England. Northeastern University was the most prolific institution with 20 publications and total citations of 9,451, followed by The Hebrew University of Jerusalem (7 publications, 2,239 citations) and Boston University (5 publications, 1,885 citations). Rockefeller University ranked fourth in terms of the number of publications (3), but had the highest average citation count per publication (805).

A total of 437 authors contributed to the top 100 cited publications on bacterial persisters. Among them, 13 first authors and 13 last authors published at least two papers. As shown in Table 5, Kim Lewis from Northeastern University was the most contributing author who published five first-author papers and 13 last-author papers. In terms of the first authors, Nathalie Q. Balaban from Rockefeller University and Iris Keren from Northeastern University both published three papers. It was worth noting that four first authors (Iris Keren; Brian P. Conlon; Tobias Dörr; Amy L. Spoering) were from Northeastern University, and the last author of their publications was Kim Lewis. For the last authors, James J. Collins from Boston University ranked second with six publications, followed by Kenn Gerdes from University of Copenhagen (five publications).

Figure 3 showed the co-occurrence network of author keywords and keywords plus. The meaningless words were manually excluded and the same meaning words were merged. The most frequently occurring keywords in the top 100 cited publications were “Escherichia coli” (57 times), “persisters” (44 times), “Pseudomonas aeruginosa” (29 times), “multidrug tolerance” (25 times), “biofilms” (25 times), “mechanism” (20 times), “stress response” (17 times). Accordingly, the keywords in the network were divided into six clusters. Four clusters were separated by the research objects, including Mycobacterium tuberculosis (red), E. coli (blue), P. aeruginosa (green), and Staphylococcus aureus (yellow). From the results of co-occurrence, current researches on bacterial persisters mainly focused on 1) the role of persisters in biofilm (yellow); and 2) the mechanism of persisters formation (purple and light blue).

A total of 12 subject categories were extracted from the WoSCC. Among them, “Microbiology” was the most frequent category with 40 publications, followed by “Multidisciplinary Sciences” with 21 publications and “Biochemistry and Molecular Biology” with 18 publications. Consistent with the number of publications, the subject categories of “Microbiology” (13,088 citations) and “Multidisciplinary Sciences” (8,427 citations) had the highest total frequency of citation. Furthermore, the subject category of “Biotechnology and Applied Microbiology” had the highest average citation count per publication (n = 471).

Discussion

In this study, a bibliometric study was performed to identify and analyze the top 100 cited publications on bacterial persisters. Commonly, the citation frequency of publication reflected the importance of the paper, which also indicated its scientific
| Rank | Title                                                                 | Journal                                      | Year | WoS | ES | GS | IF |
|------|----------------------------------------------------------------------|----------------------------------------------|------|-----|----|----|----|
| 1    | Bacterial persistence as a phenotypic switch                          | Science                                      | 2004 | 1,815 | 1,883 | 2,986 | 31.853 |
| 2    | Persister cells, dormancy and infectious disease                       | Nature Reviews Microbiology                  | 2007 | 1,239 | 1,298 | 2,118 | 14.959 |
| 3    | Persister Cells                                                        | Annual Review of Microbiology                | 2010 | 1,237 | 1,275 | 2,048 | 12.415 |
| 4    | Persistence of Mycobacterium tuberculosis in macrophages and mice requires the glyoxylate shunt enzyme isocitrate lyase | Nature                                       | 2000 | 1,032 | 1,081 | 1,607 | 25.814 |
| 5    | Platforms for antibiotic discovery                                     | Nature Reviews Drug Discovery                | 2013 | 844  | 875  | 1,553 | 37.231 |
| 6    | Mechanisms of antibiotic resistance in bacterial biofilms              | International Journal of Medical Microbiology| 2002 | 783  | 840  | 1,450 | 2.403  |
| 7    | Persister cells and tolerance to antimicrobials                        | FEMS Microbiology Letters                    | 2004 | 695  | 746  | 1,224 | 1.840  |
| 8    | Biofilms and planktonic cells of Pseudomonas aeruginosa have similar resistance to killing by antimicrobials | Journal of Bacteriology                     | 2001 | 618  | 656  | 1,103 | 3.984  |
| 9    | Specialized persister cells and the mechanism of multidrug tolerance in Escherichia coli | Journal of Bacteriology                     | 2004 | 601  | 634  | 1,021 | 4.146  |
| 10   | Distinguishing between resistance, tolerance and persistence to antibiotic treatment | Nature Reviews Microbiology                  | 2016 | 597  | 615  | 975   | 26.819 |
| 11   | Metabolite-enabled eradication of bacterial persisters by aminoglycosides | Nature                                       | 2011 | 564  | 592  | 815   | 36.280 |
| 12   | Multidrug tolerance of biofilms and persister cells                    | Current Topics in Microbiology and Immunology| 2008 | 517  | 544  | 940   | 5.102  |
| 13   | Pseudomonas aeruginosa Lifestyle: A Paradigm for Adaptation, Survival, and Persistence | Frontiers in Cellular and infection Microbiology | 2017 | 508  | 507  | 836   | 3.520  |
| 14   | Biofilm infections, their resilience to therapy and innovative treatment strategies | Journal of Internal Medicine                 | 2012 | 484  | 503  | 819   | 6.455  |
| 15   | Foamy macrophages and the progression of the human tuberculosis granuloma | Nature Immunology                            | 2009 | 481  | 504  | 840   | 26.000 |
| 16   | Ciprofloxacin Causes Persister Formation by Inducing the TisB toxin in Escherichia coli | Plos Biology                                | 2010 | 475  | 509  | 725   | 12.472 |
| 17   | Antibiotic tolerance facilitates the evolution of resistance           | Science                                      | 2017 | 472  | 483  | 706   | 41.058 |
| 18   | Silver Enhances Antibiotic Activity Against Gram-Negative Bacteria     | Science Translational Medicine               | 2013 | 458  | 451  | 656   | 14.414 |
| 19   | Recent functional insights into the role of (p)ppGpp in bacterial physiology | Nature Reviews Microbiology                  | 2015 | 440  | 443  | 669   | 24.727 |
| 20   | Internalization of Salmonella by Macrophages Induces Formation of Nonreplicating Persisters | Science                                      | 2014 | 427  | 448  | 626   | 33.611 |
| 21   | Antibiotic resistance in Pseudomonas aeruginosa: mechanisms and alternative therapeutic strategies | Biotechnology Advances                     | 2019 | 423  | 440  | 722   | 10.744 |
| 22   | Persisters: a distinct physiological state of E-coli                  | BMC Microbiology                             | 2006 | 421  | 436  | 698   | 2.896  |
| 23   | Persistent bacterial infections and persister cells                    | Nature Reviews Microbiology                  | 2017 | 418  | 428  | 657   | 31.851 |
| 24   | Activated ClpP kills persisters and eradicates a chronic biofilm infection | Nature                                      | 2013 | 416  | 430  | 617   | 42.351 |
| 25   | Molecular Mechanisms Underlying Bacterial Persisters                   | Cell                                         | 2014 | 399  | 420  | 612   | 32.242 |
| 26   | Toxin-antitoxin systems in bacterial growth arrest and persistence     | Nature Chemical Biology                      | 2016 | 392  | 410  | 574   | 15.066 |
| 27   | Mechanisms of bacterial persistence during stress and antibiotic exposure | Science                                      | 2016 | 386  | 396  | 579   | 37.205 |
| 28   | Bacterial persistence: A model of survival in changing environments    | Genetics                                     | 2005 | 384  | 392  | 650   | 4.289  |
| 29   | The challenge of treating biofilm-associated bacterial infection        | Clinical Pharmacology & therapeutics         | 2007 | 381  | 406  | 656   | 8.033  |
| 30   | Growth Rate-Dependent Global Effects on Gene Expression in Bacteria    | Cell                                         | 2009 | 375  | 400  | 663   | 31.152 |
| 31   | Bacterial persistence by RNA endonucleases                             | Proceedings of the National Academy of Sciences of the United States of America | 2011 | 373  | 397  | 553   | 9.681  |
| 32   | Nature Reviews Microbiology                                           | 2006 | 367  | 385  | 576   | 15.845 |

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### TABLE 1 (Continued) The top 100 cited studies on bacterial persisters with total citation in WoSCC, Scopus, and Google Scholar databases.

| Rank | Title                                                                 | Journal                                                                 | Year | WoS  | ES  | GS  | IF  |
|------|-----------------------------------------------------------------------|------------------------------------------------------------------------|------|------|-----|-----|-----|
| 33   | Emergence of *Pseudomonas aeruginosa* Strains Producing High Levels of Persistor Cells in Patients with Cystic Fibrosis | Journal of Bacteriology                                                 | 2010 | 361  | 381 | 577 | 3.726 |
| 34   | Dynamic Persistence of Antibiotic-Stressed Mycobacteria               | Science                                                                | 2013 | 342  | 364 | 515 | 31.477 |
| 35   | Bacterial Toxin-Antitoxin Systems: More Than Selfish Entities?        | Plos Genetics                                                          | 2009 | 339  | 374 | 654 | 9.532 |
| 36   | Bacterial Persister Cell Formation and Dormancy                       | Applied and Environmental Microbiology                                 | 2013 | 334  | 343 | 568 | 3.952 |
| 37   | Engineered bacteriophage targeting gene networks as adjuvants for antibiotic therapy | Proceedings of the National Academy of Sciences of the United States of America | 2009 | 324  | 347 | 542 | 9.432 |
| 38   | Definitions and guidelines for research on antibiotic persistence     | Nature Reviews Microbiology                                            | 2019 | 324  | 339 | 514 | 34.209 |
| 39   | Growth of *Mycobacterium tuberculosis* biofilms containing free mycopic acids and harbouring drug-tolerant bacteria | Molecular Microbiology                                                 | 2008 | 317  | 347 | 512 | 5.213 |
| 40   | Persister cells and the riddle of biofilm survival                   | Biochemistry-Moscow                                                   | 2005 | 311  | 316 | 650 | 0.858 |
| 41   | Persister formation in *Staphylococcus aureus* is associated with ATP depletion | Nature Microbiology                                                    | 2016 | 303  | 310 | 417 | N/A  |
| 42   | Cytological and transcript analyses reveal fat and lazy persistor-like bacilli in tuberculous sputum | Plos Medicine                                                         | 2008 | 294  | 229 | 442 | 12.185 |
| 43   | SOS Response Induces Persistence to Fluoroquinolones in *Escherichia coli* | Plos Genetics                                                         | 2009 | 293  | 313 | 494 | 9.532 |
| 44   | Toxins, Targets, and Triggers: An Overview of Toxin-Antitoxin Biology | Molecular Cell                                                        | 2018 | 292  | 301 | 419 | 14.548 |
| 45   | Optimization of lag time underlies antibiotic tolerance in evolved bacterial populations | Nature                                                                 | 2014 | 284  | 296 | 448 | 41.456 |
| 46   | Toxin-Antitoxin Systems Influence Biofilm and Persister Cell Formation and the General Stress Response | Applied and Environmental Microbiology                                 | 2011 | 284  | 300 | 435 | 3.829 |
| 47   | Signaling-mediated bacterial persister formation                      | Nature Chemical Biology                                                | 2012 | 278  | 294 | 417 | 12.948 |
| 48   | A Novel In Vitro Multiple-Stress Dormancy Model for *Mycobacterium tuberculosis* Generates a Lipid-Loaded, Drug- Tolerant, Dormant Pathogen | Plos One                                                              | 2009 | 277  | 294 | 423 | 4.351 |
| 49   | Characterization of the hipA7 allele of *Escherichia coli* and evidence that high persistence is governed by (p)ppGpp synthesis | Molecular Microbiology                                                | 2003 | 268  | 274 | 423 | 5.563 |
| 50   | Role of persister cells in chronic infections: clinical relevance and perspectives on anti-persister therapies | Journal of Medical Microbiology                                         | 2011 | 268  | 274 | 432 | 2.502 |
| 51   | Emergence of vancomycin tolerance in Streptococcus pneumoniae        | Nature                                                                 | 1999 | 267  | 306 | 461 | 29.491 |
| 52   | Structure-Activity Relationships for a Series of Quinoline-Based Compounds Active against Replicating and Nonreplicating *Mycobacterium tuberculosis* | Journal of Medicinal Chemistry                                      | 2009 | 265  | 265 | 324 | 4.802 |
| 53   | Microbial Persistence and the Road to Drug Resistance                | Cell Host and Microbe                                                  | 2013 | 261  | 285 | 445 | 12.194 |
| 54   | Characterization and Transcriptome Analysis of *Mycobacterium tuberculosis* Persisters | Mbio                                                                  | 2011 | 238  | 254 | 341 | 5.311 |
| 55   | Regulation of phenotypic variability by a threshold-based mechanism underlies bacterial persistence | Proceedings of the National Academy of Sciences of the United States of America | 2010 | 238  | 244 | 365 | 9.771 |
| 56   | Molecular Mechanisms of HipA-Mediated Multidrug Tolerance and Its Neutralization by HipB | Science                                                               | 2009 | 236  | 251 | 370 | 29.747 |
| 57   | New antimycobacterial drugs, regimens, and adjunct therapies: needs, advances, and future prospects | Lancet infectious Diseases                                            | 2014 | 233  | 254 | 378 | 22.433 |
| 58   | Metabolic Control of Persister Formation in *Escherichia coli*       | Molecular Cell                                                        | 2013 | 224  | 235 | 339 | 14.464 |
| 59   | ATP-Dependent Persister Formation in *Escherichia coli*              | Mbio                                                                  | 2017 | 220  | 224 | 287 | 6.689 |
| 60   | Microbial phenotypic heterogeneity and antibiotic tolerance         | Current Opinion in Microbiology                                       | 2007 | 216  | 231 | 385 | 7.654 |
| 61   | Toxin-antitoxin systems: why so many, what for?                     | Current Opinion in Microbiology                                       | 2010 | 213  | 223 | 336 | 7.714 |
| 62   | Toxin-antitoxin modules as bacterial metabolic stress managers       | Trends in Biochemical Sciences                                        | 2005 | 211  | 215 | 297 | 13.343 |

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TABLE 1 (Continued) The top 100 cited studies on bacterial persisters with total citation in WoSCC, Scopus, and Google Scholar databases.

| Rank | Title                                                                 | Journal                                         | Year | WoS | ES | GS | IF |
|------|-----------------------------------------------------------------------|-------------------------------------------------|------|-----|----|----|----|
| 63   | The antimicrobial peptide SAAP-148 combats drug-resistant bacteria and biofilms | Science Translational Medicine                   | 2018 | 207 | 208 | 241 | 17.200 |
| 64   | Role of global regulators and nucleotide metabolism in antibiotic tolerance in Escherichia coli | Antimicrobial Agents and Chemotherapy            | 2008 | 204 | 214 | 337 | 4.716 |
| 65   | Enhanced Efflux Activity Facilitates Drug Tolerance in Dormant Bacterial Cells | Molecular Cell                                   | 2016 | 202 | 205 | 303 | 14.714 |
| 66   | A new type V toxin-antitoxin system where mRNA for toxin GhoT is cleaved by antitoxin GhoS | Nature Chemical Biology                          | 2012 | 199 | 212 | 318 | 12.948 |
| 67   | Arrested Protein Synthesis Increases Persister-Like Cell Formation     | Antimicrobial Agents and Chemotherapy            | 2013 | 198 | 203 | 276 | 4.451 |
| 68   | A new class of synthetic retinoid antibiotics effective against bacterial persisters | Nature                                          | 2018 | 191 | 196 | 238 | 43.070 |
| 69   | Biofilms in periprosthetic orthopedic infections                       | Future Microbiology                               | 2014 | 187 | 187 | 294 | 4.275 |
| 70   | Persistent bacterial infections, antibiotic tolerance, and the oxidative stress response | Virulence                                        | 2013 | 182 | 185 | 309 | 3.319 |
| 71   | Phenotypic Variation of Salmonella in Host Tissues Delays Eradication by Antimicrobial Chemotherapy | Cell                                             | 2014 | 181 | 191 | 251 | 32.242 |
| 72   | Toxins H1a and CspD and small RNA regulator Hq are involved in persistor cell formation through MqsR in Escherichia coli | Biochemical and Biophysical Research Communications | 2010 | 168 | 174 | 253 | 2.595 |
| 73   | A problem of persistence: still more questions than answers?          | Nature Reviews Microbiology                       | 2013 | 168 | 177 | 266 | 23.317 |
| 74   | Identification of Anti-virulence Compounds That Disrupt Quorum-Sensing Regulated Acute and Persistent Pathogenicity | Plos Pathogens                                   | 2014 | 167 | 175 | 236 | 7.562 |
| 75   | Eradication of bacterial persisters with antibiotic-generated hydroxyl radicals | Proceedings of the National Academy of Sciences of the United States of America | 2012 | 166 | 177 | 247 | 9.737 |
| 76   | Sterilizing activities of fluoroquinolones against rifampin-tolerant populations of Mycobacterium tuberculosis | Antimicrobial Agents and Chemotherapy            | 2003 | 165 | 190 | 300 | 4.246 |
| 77   | Role of Oxidative Stress in Persister Tolerance                       | Antimicrobial Agents and Chemotherapy            | 2012 | 164 | 179 | 254 | 4.565 |
| 78   | Increased persistence in Escherichia coli caused by controlled expression of toxins or other unrelated proteins | Journal of Bacteriology                          | 2006 | 163 | 172 | 261 | 3.993 |
| 79   | Formation, physiology, ecology, evolution and clinical importance of bacterial persisters | FEMS Microbiology Reviews                        | 2017 | 163 | 168 | 254 | 11.392 |
| 80   | Targeting Persisters for Tuberculosis Control                         | Antimicrobial Agents and Chemotherapy            | 2012 | 163 | 163 | 270 | 4.565 |
| 81   | Ectopic overexpression of wild-type and mutant hipA genes in Escherichia coli: Effects on macromolecular synthesis and persister formation | Journal of Bacteriology                          | 2006 | 162 | 166 | 263 | 3.993 |
| 82   | Role of persisters and small-colony variants in antibiotic resistance of planktonic and biofilm-associated Staphylococcus aureus: an in vitro study | Journal of Medical Microbiology                   | 2009 | 160 | 174 | 280 | 2.272 |
| 83   | Phenotypic bistability in Escherichia coli’s central carbon metabolism | Molecular Systems Biology                         | 2014 | 158 | 164 | 248 | 10.872 |
| 84   | Starvation, Together with the SOS Response, Mediates High Biofilm-Specific Tolerance to the Fluoroquinolone Ofloxacin | Plos Genetics                                    | 2013 | 157 | 170 | 262 | 8.167 |
| 85   | Multiple Toxic-Antitoxin Systems in Mycobacterium tuberculosis         | Toxins                                           | 2014 | 157 | 155 | 216 | 2.938 |
| 86   | HipA-mediated antibiotic persistence via phosphorylation of the glutamyl-tRNA-synthetase | Nature Communications                            | 2013 | 156 | 166 | 229 | 10.742 |
| 87   | Pseudomonas aeruginosa Increases Formation of Multidrug-Tolerant Persister Cells in Response to Quorum-Sensing Signaling Molecules | Journal of Bacteriology                          | 2010 | 155 | 176 | 272 | 3.726 |
| 88   | Evaluation of short synthetic antimicrobial peptides for treatment of drug-resistant and intracellular Staphylococcus aureus | Scientific Reports                                | 2016 | 154 | 158 | 192 | 4.259 |
| 89   | Isocitrate lyase mediates broad antibiotic tolerance in Mycobacterium tuberculosis | Nature Communications                            | 2014 | 154 | 168 | 217 | 11.470 |
| 90   | PhoU is a persistence switch involved in persister formation and tolerance to multiple antibiotics and stresses in Escherichia coli | Antimicrobial Agents and Chemotherapy            | 2007 | 154 | 157 | 244 | 4.390 |

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The citation frequency of each publication was between 2009 and 2014 indicated that more attention was paid to the field of bacterial persisters by researchers, or there were several important scientific breakthroughs during this period. The growth rate of citations increased significantly after 2009 also reflecting increasing research interest in bacterial persisters.

In this study, the top 100 cited papers on bacterial persisters were published between 1997 and 2019. Among them, 2009 to 2014 was the productive period of highly cited publication on bacterial persisters (a total of 52 publications), and 2013 was found to have the most publications. The increase of publications between 2009 and 2014 indicated that more attention was paid to the field of bacterial persisters by researchers, or there were several important scientific breakthroughs during this period. The growth rate of citations increased significantly after 2009 also reflecting increasing research interest in bacterial persisters.

The citation frequency of each publication was between 147 and 1815 (WoSCC); 153 and 1883 (Scopus); 207 and 2,986 (Google Scholar). The number of citations per publication showed significant differences between databases. The research on bacterial persisters started more than 80 years ago when Hobby and Bigger found that penicillin could not fully kill culture (Hobby et al., 1942; Bigger, 1944). Therefore, the WoSCC was selected as the benchmark as it included citation metrics from 1900 to the present. The Scopus currently included citations starting in 1960, and this is a deficiency in analyzing the most cited publications (Jafarzadeh et al., 2015). Google Scholar showed higher citation frequencies as it included books, conference proceedings, dissertations, technical reports, and preprints, in addition to scientific papers (Jafarzadeh et al., 2015; Ahmad et al., 2019).

Generally speaking, earlier publications had more time to be cited and likely achieved more citations (Picknett and Davis, 1999; Jiang et al., 2019). However, our analysis discovered that the total citation counts were not related statistically to the age of publication, which was similar to the results of other bibliometric analysis (Ahmad et al., 2019; Jiang et al., 2019). The reason might be that earlier publications are possibly no longer cited as they were absorbed by new knowledge, and publications without persistent importance are more likely to be forgotten with increasing time (Garfield, 1987; Paladugu et al., 2002). Another explanation was that researchers showed more interest in the latest developments which might give in-depth research results or trigger new research directions. This viewpoint was verified by the decreasing trend in mean citation per year with age increasing.

All the top-cited papers on bacterial persisters were published in English, that’s probably because English is the most widely used language in knowledge dissemination, and several databases had a preference for English language (Seglen, 1997b; Bondi, 2017; Zhang et al., 2021). Moreover, as institutions in

**TABLE 1 (Continued) The top 100 cited studies on bacterial persisters with total citation in WoSCC, Scopus, and Google Scholar databases.**

| Rank | Title                                                                 | Journal                                      | Year | WoS⁣ | ES⁤ | GS⁥ | IF⁦ |
|------|----------------------------------------------------------------------|----------------------------------------------|------|------|-----|-----|-----|
| 91   | Persistence of Borrelia burgdorferi in Rhesus Macaques following     | Plos One                                     | 2012 | 153  | 156 | 242 | 3.730 |
| 92   | Persister cells, the biofilm matrix and tolerance to metal cations in | Environmental Microbiology                   | 2005 | 153  | 162 | 246 | 4.559 |
| 93   | Dormancy Is Not Necessary or Sufficient for Bacterial Persistence    | Antimicrobial Agents and Chemotherapy        | 2013 | 151  | 155 | 230 | 4.451 |
| 94   | Bridging the gap between viable but non-culturable and antibiotic    | Trends in Microbiology                       | 2015 | 151  | 167 | 238 | 9.500 |
| 95   | Biofilm-related disease                                             | Expert Review of Anti-infective therapy      | 2018 | 149  | 155 | 228 | 3.090 |
| 96   | Letting Sleeping dogs Lie: Does Dormancy Play a Role in Tuberculosis?| Annual Review of Microbiology, Vol 64, 2010  | 2010 | 149  | 162 | 265 | N/A  |
| 97   | Carbon Sources Tune Antibiotic Susceptibility in *Pseudomonas        | Cell Chemical Biology                        | 2017 | 148  | 156 | 201 | 5.592 |
| 98   | Bacterial persistence and expression of disease                      | Clinical Microbiology Reviews                | 1997 | 148  | 146 | 275 | 8.585 |
| 99   | GlpD and PhoP participate in persister cell formation in *Escherichia| Journal of Bacteriology                     | 2006 | 147  | 145 | 237 | 3.993 |
| 100  | Kinase activity of overexpressed HipA is required for growth arrest  | Journal of Bacteriology                     | 2006 | 147  | 153 | 217 | 3.993 |

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¹WoS represented WoSCC database;
²ES represented Elsevier Scopus database.
³GC represented Google Scholar database.
⁴IF showed the IF of journal in the year of publication, and the N/A represented that the journal IF had not been assigned in the year of publication.

recognition by researchers in the relevant field, and how it generated discussion or triggered new research direction (Fardi et al., 2017; Tarazona et al., 2018). Moreover, the highly cited publication was suggested as a milestone study in the related field (Van Noorden et al., 2014). Hence, the top 100 cited publications included in this study could be identified as “classics” in the field of bacterial persisters, and the bibliometric analysis of “classics” emphasized researchers, research outputs, and future research trends (Godin, 2006).
TABLE 2 Journals of the top 100 cited publications on bacterial persisters.

| Journal                                             | Number of publications | Total citations | Average citation count per paper | 2021 IF |
|-----------------------------------------------------|------------------------|-----------------|----------------------------------|---------|
| Journal of Bacteriology                            | 8                      | 2,354           | 294                              | 3.476   |
| Nature Reviews Microbiology                        | 7                      | 3,553           | 508                              | 78.297  |
| Antimicrobial Agents and Chemotherapy              | 7                      | 1,199           | 171                              | 5.938   |
| Nature                                              | 6                      | 2,754           | 459                              | 69.504  |
| Science                                             | 6                      | 3,678           | 613                              | 63.798  |
| Proceedings of the National Academy of Sciences    | 4                      | 1,101           | 275                              | 12.779  |
| Cell                                                | 3                      | 955             | 318                              | 66.85   |
| Molecular Cell                                      | 3                      | 718             | 239                              | 19.328  |
| Nature Chemical Biology                            | 3                      | 869             | 289                              | 16.29   |
| Plos Genetics                                       | 3                      | 789             | 263                              | 6.02    |
| Science Translational Medicine                      | 2                      | 665             | 332                              | 19.359  |
| Nature Communications                               | 2                      | 310             | 155                              | 17.694  |
| Annual Review of Microbiology                       | 2                      | 1,386           | 693                              | 16.232  |
| Mbio                                                | 2                      | 458             | 229                              | 7.786   |
| Current Opinion in Microbiology                     | 2                      | 429             | 214                              | 7.584   |
| Applied and Environmental Microbiology              | 2                      | 618             | 309                              | 5.005   |
| Molecular Microbiology                              | 2                      | 585             | 292                              | 3.979   |
| Plos One                                            | 2                      | 430             | 215                              | 3.752   |
| Journal of Medical Microbiology                     | 2                      | 428             | 214                              | 3.196   |
| Nature Reviews Drug Discovery                       | 1                      | 844             | 844                              | 112.288 |
| Lancet Infectious Diseases                         | 1                      | 233             | 233                              | 71.421  |
| Clinical Microbiology Reviews                       | 1                      | 148             | 148                              | 50.129  |
| Cell Host and Microbe                              | 1                      | 261             | 261                              | 31.316  |
| Nature Immunology                                   | 1                      | 481             | 481                              | 31.25   |
| Nature Microbiology                                 | 1                      | 303             | 303                              | 30.964  |
| Trends in Microbiology                              | 1                      | 151             | 151                              | 18.23   |
| Biotechnology Advances                              | 1                      | 423             | 423                              | 17.681  |
| FEMS Microbiology Reviews                          | 1                      | 163             | 163                              | 15.177  |
| Trends in Biochemical Sciences                      | 1                      | 211             | 211                              | 14.264  |
| Journal of Internal Medicine                        | 1                      | 484             | 484                              | 13.068  |
| Molecular Systems Biology                           | 1                      | 158             | 158                              | 13.068  |
| Plos Medicine                                       | 1                      | 294             | 294                              | 11.613  |
| Plos Biology                                        | 1                      | 475             | 475                              | 9.593   |
| Cell Chemical Biology                               | 1                      | 148             | 148                              | 9.039   |
| Journal of Medicinal Chemistry                      | 1                      | 265             | 265                              | 8.039   |
| Plos Pathogens                                      | 1                      | 167             | 167                              | 7.464   |
| Clinical Pharmacology & therapeutics                | 1                      | 381             | 381                              | 6.903   |
| Frontiers in Cellular and infection Microbiology    | 1                      | 508             | 508                              | 6.073   |
| Expert Review of Anti-infective therapy             | 1                      | 149             | 149                              | 5.854   |
| Environmental Microbiology                          | 1                      | 153             | 153                              | 5.476   |
| Virulence                                           | 1                      | 182             | 182                              | 5.428   |
| Toxins                                              | 1                      | 157             | 157                              | 5.075   |
| Scientific Reports                                  | 1                      | 154             | 154                              | 4.996   |
| Current Topics in Microbiology and Immunology       | 1                      | 517             | 517                              | 4.737   |
| BMC Microbiology                                    | 1                      | 421             | 421                              | 4.465   |
| Genetics                                            | 1                      | 384             | 384                              | 4.402   |
| International Journal of Medical Microbiology       | 1                      | 783             | 783                              | 3.658   |

(Continued on following page)
**TABLE 2 (Continued) Journals of the top 100 cited publications on bacterial persisters.**

| Journal                                      | Number of publications | Total citations | Average citation count per paper | 2021 IF |
|----------------------------------------------|------------------------|----------------|----------------------------------|---------|
| Future Microbiology                          | 1                      | 187            | 187                              | 3.553   |
| Biochemical and Biophysical Research Communications | 1                      | 168            | 168                              | 3.322   |
| Biochemistry-Moscow                          | 1                      | 311            | 311                              | 2.824   |
| FEMS Microbiology Letters                    | 1                      | 695            | 695                              | 2.82    |

**TABLE 3 Countries of the top 100 cited publications on bacterial persisters.**

| Country                      | Number of publications | Total citations | Average citation count |
|------------------------------|------------------------|-----------------|------------------------|
| United States                | 64                     | 23,130          | 361                    |
| England                      | 8                      | 2,676           | 334                    |
| Israel                       | 7                      | 2,239           | 320                    |
| Belgium                      | 5                      | 1,194           | 239                    |
| Switzerland                  | 3                      | 681             | 227                    |
| Sweden                       | 2                      | 924             | 462                    |
| Denmark                      | 2                      | 678             | 339                    |
| Canada                       | 2                      | 576             | 288                    |
| France                       | 2                      | 314             | 157                    |
| New Zealand                  | 1                      | 508             | 508                    |
| Netherlands                  | 1                      | 207             | 207                    |
| China                        | 1                      | 202             | 202                    |
| India                        | 1                      | 160             | 160                    |
| Spain                        | 1                      | 149             | 149                    |

*The country distributions were extracted based on the country of first author.*

**TABLE 4 Institutions with more than two papers in the top 100 cited publications on bacterial persisters.**

| Institution                  | Country         | Number of publications | Total citations | Average citation count |
|------------------------------|-----------------|------------------------|-----------------|------------------------|
| Northeastern University      | United States   | 20                     | 9,451           | 472                    |
| The Hebrew University of Jerusalem | Israel         | 7                      | 2,239           | 320                    |
| Boston University            | United States   | 5                      | 1,885           | 377                    |
| The Rockefeller University   | United States   | 3                      | 2,415           | 805                    |
| Harvard University           | United States   | 3                      | 464             | 155                    |
| University of North Dakota   | United States   | 2                      | 430             | 215                    |
| University of Illinois       | United States   | 2                      | 428             | 214                    |
| Tulane University            | United States   | 2                      | 301             | 150                    |
| Texas A&M University         | United States   | 2                      | 452             | 226                    |
| Princeton University         | United States   | 2                      | 375             | 188                    |
| Pennsylvania State University | United States   | 2                      | 532             | 266                    |
| Newcastle University         | England         | 2                      | 772             | 386                    |
| Johns Hopkins University     | United States   | 2                      | 317             | 158                    |
| Brown University             | United States   | 2                      | 583             | 292                    |
| Broad Institute of MIT & Harvard | United States   | 2                      | 348             | 174                    |

*The institution distributions were extracted based on the institution of first author.*
TABLE 5 Authors with more than two first-author or last-author publications in the top 100 cited publications on bacterial persisters.

| First author         | Institution                      | Number of papers |
|----------------------|----------------------------------|------------------|
| Kim Lewis            | Northeastern University           | 5                |
| Nathalie Q. Balaban  | The Rockefeller University        | 3                |
| Iris Keren           | Northeastern University           | 3                |
| Brian P. Conlon      | Northeastern University           | 2                |
| Jose Luis Del Pozo   | Clinical University of Navarra    | 2                |
| Tobias Dier          | Northeastern University           | 2                |
| Sarah Schmidt Grant  | Broad Institute of MIT & Harvard  | 2                |
| Alexander Harms      | University of Copenhagen          | 2                |
| Shaleen B. Korch     | University of North Dakota        | 2                |
| Etienne Maisonneuve  | Newcastle University              | 2                |
| Amy L. Spoering      | Northeastern University           | 2                |
| Laurence Van Melderen| University of Libre Bruxelles     | 2                |
| Xiaoxue Wang         | Brown University                  | 2                |

| Last author          | Institution                      | Number of papers |
|----------------------|----------------------------------|------------------|
| Kim Lewis            | Northeastern University           | 13               |
| James J. Collins     | Boston University                 | 6                |
| Kenn Gerdes          | University of Copenhagen         | 5                |
| Nathalie Q. Balaban  | The Hebrew University of Jerusalem| 4                |
| Thomas K. Wood       | Texas A&M University              | 4                |
| John D. McKinney     | The Hebrew University of Jerusalem| 3                |
| Michael R. Barer     | University of London              | 2                |
| Mark P. Brynildsen   | Princeton University              | 2                |
| Thomas M. Hill       | University of North Dakota        | 2                |
| Deborah T. Hung      | Broad Institute MIT & Harvard     | 2                |
| Stanislas Leibler    | The Rockefeller University        | 2                |
| Jan Michiels         | Katholieke University Leuven      | 2                |
| Marin Vulić           | Northeastern University           | 2                |

United States and England made significant contributions to the field of bacterial persisters, researchers from these institutions might prefer to cite papers published in English. Among the top 100 cited publications, the number of origin articles (64) was more than review articles (35). Meanwhile, the review articles had a higher average citation count per paper \( n = 377 \) than origin articles \( n = 317 \). Review articles generally have higher citations than other types \( \text{Seglen, 1997a} \). The results also reflected that review articles were important for researchers to convey their points of view, even though new findings in origin articles have gained significant attention. We found that 62 publications were included in “Microbiology” and “Multidisciplinary Sciences” subject categories, while “Biochemistry and Molecular Biology” was the focus of 18 publications. These indicated that researches on bacterial persisters involved the cross of multi-disciplinary and researchers have been working to explore the molecular mechanisms of persisters formation.

According to our bibliometric analysis, 51 different journals published the top 100 cited publications on bacterial persister. Some of the top 100 cited papers were published in journals focusing on molecular biology or pharmacy, like Molecular Cell, Nature Chemical Biology, and Nature Reviews Drug Discovery. This was also related to the opinion that multi-disciplinary researches have increasingly concerned with the problem of bacterial persisters. In terms of IFs, 51 papers were published in journals with 2021 IFs more than 10, and 77 papers in journals had 2021 IFs more than 5. However, the Journal of Bacteriology, which published the highest number of papers in the top 100 cited list, had a relatively low IF \( 3.476 \). In addition, more than half of the top papers (51) were published in journals specializing in microbiology. These facts suggested that most researchers in the field of bacterial persisters were more favored to choose reputational and authoritative journals in their research field, not only focusing on IFs. Several other factors also influenced authors to choose journals, including the difficulty of manuscript acceptance, publication charges, time of peer review and so on \( \text{Jiang et al., 2019; Shamsi et al., 2021} \). On the other hand, the publication cycle time and circulation time of journals also affected the citations of papers. Usually, publications in journals with a short publication cycle time and long circulation time likely gained more citation times \( \text{Jiang et al., 2019} \). Furthermore, journal accessibility had an impact on the citation of publications \( \text{Eysenbach, 2006} \).

More than half of the top 100 cited publications (64 publications) were published in the United States, while England ranked second with eight publications. In several other bibliometric studies of similar fields, the highest number of papers was also published in the United States \( \text{Arshad et al., 2020; Liu et al., 2020; Zhu et al., 2020} \). This reflected the great influence of the United States in the field of pathogenic bacteria. This was probably because the United States with high GDP allocates more research funding to scientific investigation and some of the world’s top research institutions are located in the United States \( \text{Peng et al., 2021; Zhang et al., 2021} \). Besides, authors in the United States were easier to publish their studies in American journals, and they tend to cite local publications \( \text{Paladugu et al., 2002; Peng et al., 2021} \). Furthermore, there were 13 institutions from the United States in the list of institutions with more than two publications, while the rest two institutions were in Israel and England respectively. Among these institutions, the studies on bacterial persisters
were mainly from universities, and only one research institution called Broad Institute of MIT & Harvard. Significantly, Peking University in China had one paper in the list of top 100 cited publications, and this represented the progress in the influence of our national scientific research. Previous studies have proved that China led the scientific production in several bacterial fields, however, the quality of publications from China should be further improved (Zhu et al., 2020; Quincho-Lopez and Pacheco-Mendoza, 2021).

Kim Lewis from Northeastern University was the most prolific author with the most number of publications both as first author and last author. His studies on bacterial persisters are mainly focusing on the physiological characteristics of persisters (Shah et al., 2006) and factors affecting the formation of persisters, like oxidative stress (Wu et al., 2012), ATP dependent (Conlon et al., 2016; Shan et al., 2017), antibiotics (Doerr et al., 2010), toxin/antitoxin (Correia et al., 2006; Doerr et al., 2010). Besides, Kim Lewis is also devoted to identifying novel targets or compounds to kill persisters and eradicate persistent infections (Conlon et al., 2013; Lewis, 2013). In addition, Kim Lewis cooperated with some productive authors, like Nathalie Q. Balaban from Rockefeller University, Tobias Dörr from Northeastern University, and Marin Vulić from Northeastern University.

Keywords are highly refined research content and they provide research topics and hotspots in the field. It was worth noting that keywords are not required in every publication and several papers did not display author keywords (Harms et al., 2018; Kim et al., 2018; Balaban et al., 2019). Therefore, the keywords plus from the WoSCC database were utilized to form a relatively complete network. The keywords “Escherichia coli”, “Pseudomonas aeruginosa”, “Mycobacterium tuberculosis” and “Staphylococcus aureus” occurred more than 10 times, and this indicated that researches on bacterial persisters were mainly based on studies of these strains. In addition, the high-frequency keywords belong to the mechanism of persisters formation.
persistors (McKinney et al., 2000; Hansen et al., 2008; metabolism were involved in the formation of bacterial metabolism, nucleotide metabolism, and fatty acids reduced metabolism. It has been reported that carbon (2022). Furthermore, Bacterial persisters are in a state of (p)ppGpp synthesis (Korch et al., 2003)(Moyed and synthesis, and peptidoglycan synthesis, as well as induction of (p)ppGpp stringent response, messenger RNA, “oxidative stress” were ranked in sequence. Phenotypic heterogeneity is generated by epigenetic regulation and it leads to the formation of nonreplicating persisters under fluctuating selective perssures (Dhar and McKinney, 2007; Helaine et al., 2014). This can be distinguished from the mechanism of bacterial resistance which is acquired by mutations or horizontal gene transfer of resistance genes (Balaban et al., 2019). The keywords “stress response,” “messenger RNA” and “oxidative stress” were also linked to “phenotypic heterogeneity.” This was probably because the phenotypic growth arrest of persisters was generated by activating stress responses. Several stress response pathways were linked to the formation of persisters, including oxidative stress, (p)ppGpp stringent response, messenger RNA involved in Toxin-antitoxin system, SOS response (Doerr et al., 2009; Vega et al., 2012; Wu et al., 2012; Maisonneuve and Gerdes, 2014; Sala et al., 2014). Keywords “inhibition,” “peptidoglycan,” “murein synthesis,” and “DNA synthesis” in the light blue cluster were related to the toxin protein HipA, which is a member of the bacterial toxin-antitoxin modules. The hipA gene regulated the establishment of a persistent state through inhibition of murein synthesis, DNA synthesis, and peptidoglycan synthesis, as well as induction of (p)ppGpp synthesis (Korch et al., 2003)(Moyed and Bertrand, 1983). The development of compounds that interfered with these pathways was an alternative strategy to kill persisters (Tkachenko et al., 2021; Kaushik et al., 2022). Furthermore, Bacterial persisters are in a state of reduced metabolism. It has been reported that carbon metabolism, nucleotide metabolism, and fatty acids metabolism were involved in the formation of bacterial persisters (McKinney et al., 2000; Hansen et al., 2008; Kotte et al., 2014). Therefore, the combination of metabolic stimuli and antibiotics (like aminoglycosides) enhanced the ability to kill persisters (Allison et al., 2011). The role of persisters in biofilms has been extensively studied, and the keyword “biofilms” was linked to 51 (63.8%) keywords. There were strong link strengths between “biofilms” and “persisters,” this was because biofilms induce the formation of persisters, and persisters in biofilm are largely responsible for the resistance of biofilms (Lewis, 2001). Several keywords, like “toxin antitoxin system,” “stress response,” “messenger RNA,” and “oxidative stress” were linked to both “mechanism” and “biofilms.” During pathogenesis, bacteria often form a mature three-dimensional biofilm architecture through secreting extracellular matrix and cell division. In biofilms, bacteria are under the condition of nutrient limitation and therefore activating the (p)ppGpp involved stress response and triggering toxin-mediated antibiotic tolerance (Nguyen et al., 2011; Maisonneuve and Gerdes, 2014). These render the bacterial population less susceptible to antibiotics in the microenvironment conditions of biofilms, and also facilitated the formation of persisters in biofilms (Wang and Wood, 2011; Romling and Balsalobre, 2012). In addition, there were several antimicrobial agents linked to the keyword “biofilms,” such as “antibiotic,” “tobramycin,” and “beta-lactam.” Although persisters and biofilms were tolerant to antimicrobial (Keren et al., 2004), the use of antibiotics in combination with compounds to eradicate both persisters and biofilms has become a possible therapeutic strategy. For example, manifests enhanced the activity of tobramycin against P. aeruginosa infections (Meylan et al., 2017). However, there were relatively few keywords concerning strategies against persisters. The main reason was that the specific regulatory network for persister formation was not particularly clear. This led to few efficient targets for the development of novel inhibitors. In-depth mechanism studies were urgently needed and it continued to be the future hot spot. Furthermore, the identification of compounds with novel targets against persisters was helpful to solve the problem of chronic infection in the clinic.

To our knowledge, this study was the first bibliometric analysis to identify the top 100 cited publications on bacterial persisters. There were some limitations as with other bibliometric analyses. First, the truncated search terms “persisters,” “persisters” and “tolerant” were utilized to define the research topics in the WoSCC database, some related publications were not included in the analysis as the diversity of the keywords. Second, although the literature search had no language restriction, it appears that only English-language studies were included in the bibliometric analysis. There were language biases in this study. Third, the top 100 cited publications were sorted by the number of total citations, while the citation frequency of publications is affected by several factors, like authors, institutions, language, and journals’ IF. In addition, earlier publications tend to achieve more citations, and some recent papers with high academic value were out of consideration as they don’t have enough time to accumulate citations. Regardless
of publication year, the mean citation per year was an alternative indicator to identify the most influential publication. Moreover, self-citations have a substantial influence on the citation-based metric and this might introduce potential bias in bibliometrics. Finally, this study was a cross-sectional study and the identified top 100 cited publications could change in the future.

Conclusion

We performed a bibliometric study of the top 100 cited publications related to bacterial persisters. These papers were published from 1997 to 2019 in 51 journals and the citation frequency of these publications presented a rising trend. The United States contributed greatly to the highly cited publications on bacterial persisters. Professor Kim Lewis from Northeastern University was the most productive author. Based on the results of keywords co-occurrence, it was found that the researches on bacterial persisters mainly focused on exploring the mechanism of persister formation or re-growth. This study provided research trends on bacterial persisters, and these might help researchers and clinical workers to better understand the classic studies and new findings in this field.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

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Author contributions

YJ contributed to design and perform the experiment, as well as write the original draft. HL, PZ, and PX contributed to screen the publications and visualizing analysis. LS and YB contributed to analyze the data and formal analysis. PY and YZ contributed to review and edit the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.1001861/full#supplementary-material
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