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ORIGINAL RESEARCH

Bibliometric and Visualization Analysis of DprE1 Inhibitors to Combat Tuberculosis

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Background: Tuberculosis (TB) poses a serious threat to public health, particularly owing to the increase in multidrug-resistant tuberculosis (MDR-TB) and extremely drug-resistant tuberculosis (XDR-TB); thus, there is an imperative need for novel treatments to tackle this issue. Decaprenylphosphoryl-β-D-ribose 2′-epimerase (DprE1) is essential for mycobacterial cell wall integrity and viability. As no relevant bibliometric study has been reported, we performed bibliometric and visual analyses to depict the knowledge framework of research related to the involvement of DprE1 in TB.

Methods: Relevant studies were sourced from the Web of Science Core Collection database. VOSviewer, CiteSpace, and bibliometrics (http://bibliometric.com/) were used to construct networks based on an analysis of journals, countries, funding, institutions, authors, references, and keywords.

Results: A total of 184 publications were retrieved; the total citations were 3405 times and the mean citation was 17.28 per article. The annual number of publications on DprE1 in TB has shown a significantly increasing trend. The European Journal of Medicinal Chemistry is the most published journal, with 19 articles. Lu Yu and Bin Wang contributed the most prolific authors with 18 articles. Stratified by the number of publications, India was the most prolific country that cooperated closely with the USA, UK, Japan, and United Arab Emirates. Burstness analysis of references and keywords showed that the developing research trends in this field mainly woven around "Mtb", "DprE1" and "inhibitors" during the past years.

Conclusion: A systematic bibliometric study indicates that DprE1 remains a focal point in the anti-TB domain. These results can serve as a data-driven reference for future research and offer precise insights into the development of anti-TB agents associated with DprE1. To the best of our knowledge, this study is the first to comprehensively investigate DprE1 in TB by means of bibliometric analysis.

Keywords: DprE1 inhibitors, tuberculosis, drug target, CiteSpace, VOSviewer, R-bibliometrix

Introduction

TB is an infectious disease caused by the bacillus of Mtb, which accounted for 1.25 million fatalities in 2023 according to Global Tuberculosis Report 2024, particularly due to the COVID 19 pandemic during the 2020–2022 period, TB programs all over the world faced major setbacks.[1] It is evident that TB is the primary cause of mortality among those with HIV, exceeding HIV itself as the foremost infectious illness fatality. In the past decades, the swift proliferation of drug-resistant strains, such as MDR- and XDR-TB, together with the increase in co-infections with pulmonary TB and HIV[2,3] has brought new obstacles to TB prevention and control.

Although the World Health Organization (WHO) has announced a program for the eradication of TB by 2050, achieving this ambitious goal necessitates the acceleration of the decline in TB incidence to 15% per year, as opposed to the current rate of 4–5% per year.[1,4–6] To achieve global control of this epidemic, there is an unmet need for new pharmaceuticals with novel mechanisms of action to completely eradicate TB.[7]

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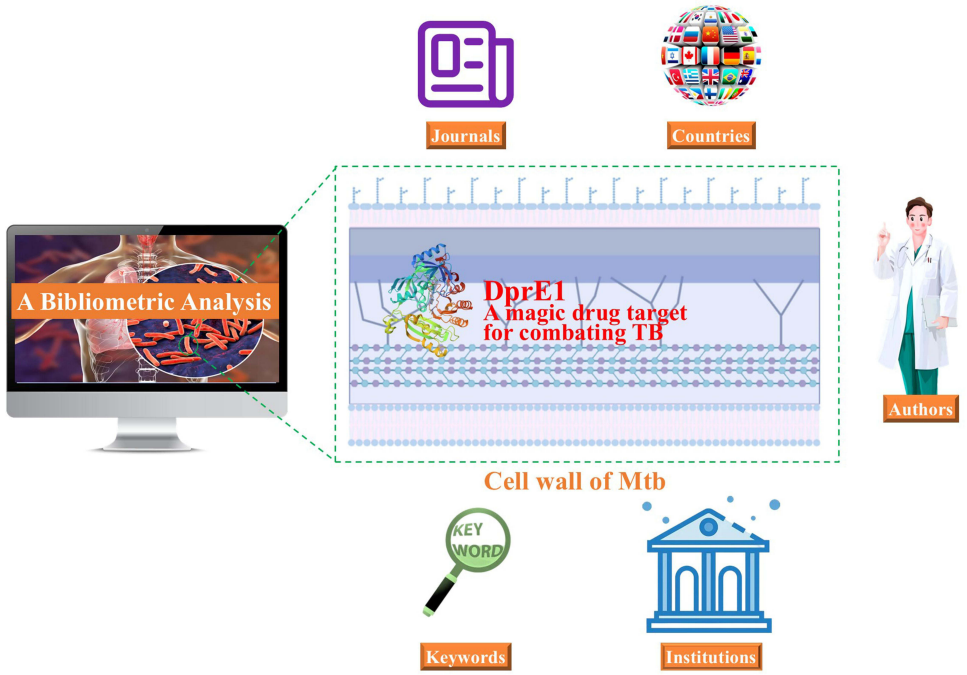
Graphical Abstract



The cell envelope of Mtb has received considerable attention in this context. The cell walls of mycobacteria are distinctive, with an exterior mycolic acid layer cooperating with peptidoglycan via an arabinogalactan layer (Figure 1). Indeed, there are numerous anti-TB medications (commercial pharmaceutical preparations for the treatment of TB) that target the cell wall biosynthesis pathway, including both the first and second lines of anti-TB drugs, such as isoniazid, which specifically targets InhA, an enzyme involved in mycolic acid biosynthesis.[8] Ethambutol functions by competing with the substrates for binding to the arabinosyltransferases EmbB and EmbC subunits.[9]

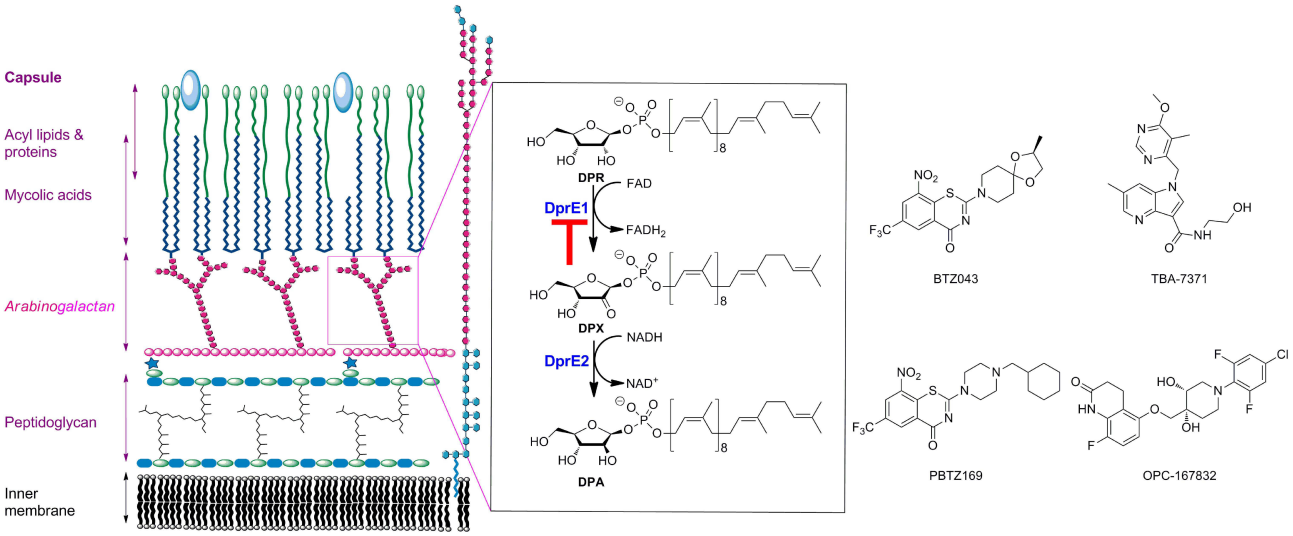


Figure 1 Schematic structure of the *M. tuberculosis* cell wall. DprE1 catalyzes the oxidation of DPR to DPX and representative inhibitors of DprE1.

In a groundbreaking study, decaprenylphosphoryl-β-D-ribose 2′-epimerase (or decaprenylphosphoryl-β-D-ribofuranose 2-oxidase, DprE1, *rv3790c*) was firstly reported by Christophe et al[10] and Makarov et al,[11] and considered as an innovative and highly promising therapeutic target for the development of new anti-TB pharmaceuticals, and been regarded as a "magic drug target." Thus, DprE1 is a novel validated target in the Mtb cell wall that might be further exploited to facilitate the discovery of new drugs to hinder Mtb proliferation, and already been validated as an appealing drug target for treatment of TB (Figure 1).[12–16] Lipoarabinomannan and the peptidoglycan-arabinogalactan-mycolic acid (PAM) complex are the primary and unique components of the Mtb cell wall. Peptidoglycan is connected to arabinogalactan in the PAM complex, which subsequently incorporates mycolic acid into its cell wall. Lipoarabinomannan consists of mannopyranosyl residues and d-arabinofuranose, which are essential components in a wide range of metabolic pathways. Decaprenylphosporyl arabinose serves as a substrate for arabinosyltransferase and is crucial for the synthesis of mycobacterial cell wall polysaccharides including lipoarabinomannan and arabinogalactan. DprE1 belongs to the flavoprotein family and facilitates the oxidation of decaprenylphosphoryl-D-ribose (DPR) to decaprenylphosphoryl-2-ketoribose (DPX), which is later reduced to DPA by the enzyme DprE2 (*rv3791c*) (Figure 1).

Among the developed DprE1 inhibitors, benzothiazinone is probably the most prominent parent compound.[17] In the course of this study, a diversity of its derivatives were developed (Figure 1), such as BTZ043 and PBTZ169 (macozinone), along with TBA-7371 and OPC-167832, all of which are currently being evaluated in clinical trials.[13,18–21] In view of the promising drug-like profile of DprE1 inhibitors, potential anti-TB drugs could be further explored.

Given the rapid progress in the study of the role of DprE1 in TB, it is essential to comprehensively investigate recent advances and perspectives on this subject. Bibliometrics is a prevalent strategy to illustrate the knowledge framework and frontiers of a discipline. Although several excellent reviews have examined the correlation between DprE1 and TB,[22–29] a bibliometric analysis has not yet been conducted in this domain. Therefore, in this study, we performed bibliometric and visual analyses to compile a comprehensive overview of publications since 2010. This study intends to provide an overview of research on the links between DprE1 and TB, and serves as a valuable reference for researchers to better examine the historical background and future trajectories in this field. More importantly, this study emphasized the advancement of DprE1 inhibitors (a substance that inhibits DprE1 enzyme, hindering Mtb cell wall biosynthetic pathway) for combating Mtb precisely, with a straightforward focus on this enzyme.

Methods

Data Acquisition

Data were retrieved on December 25, 2024, from the Web of Science Core Collection (WoSCC), and the search formula was set to TS = (tuberculosis* OR TB*) AND TS = (DprE1* OR decaprenylphosphoryl-β-D-ribose 2′-epimerase* OR decaprenylphosphoryl-β-D-ribofuranose 2-oxidase*). Non-English studies were excluded, and the timeframe was established to incorporate a 15-year period from 2010 to 2024. In our study, one irrelevant document (book chapter) was excluded and only articles, reviews, and letters were included (Figure 2).

Evaluation Indicators

In this study, indicators such as relevant quantities and development situations of publications, citations, journals, countries, funding, institutions, authors, co-author, co-institution, co-country, highly cited studies, co-cites references, references burst, keyword co-occurrence, keyword clustering, and keyword burst were used to depict the research hotspots of DprE1.

Data Analysis

In this study, bibliometric and visual analyses were conducted using VOSviewer, CiteSpace, and a bibliometric website (http://bibliometric.com/).

VOSviewer (version 1.6.20) is a software application extensively employed in bibliometric analysis, which is exploited by Professor Nees Jan van Eck and Ludo Waltman.[30] It has a robust capability for the generation and visualisation of bibliometric networks, including the co-occurrence, co-authorship, and co-citation network maps of

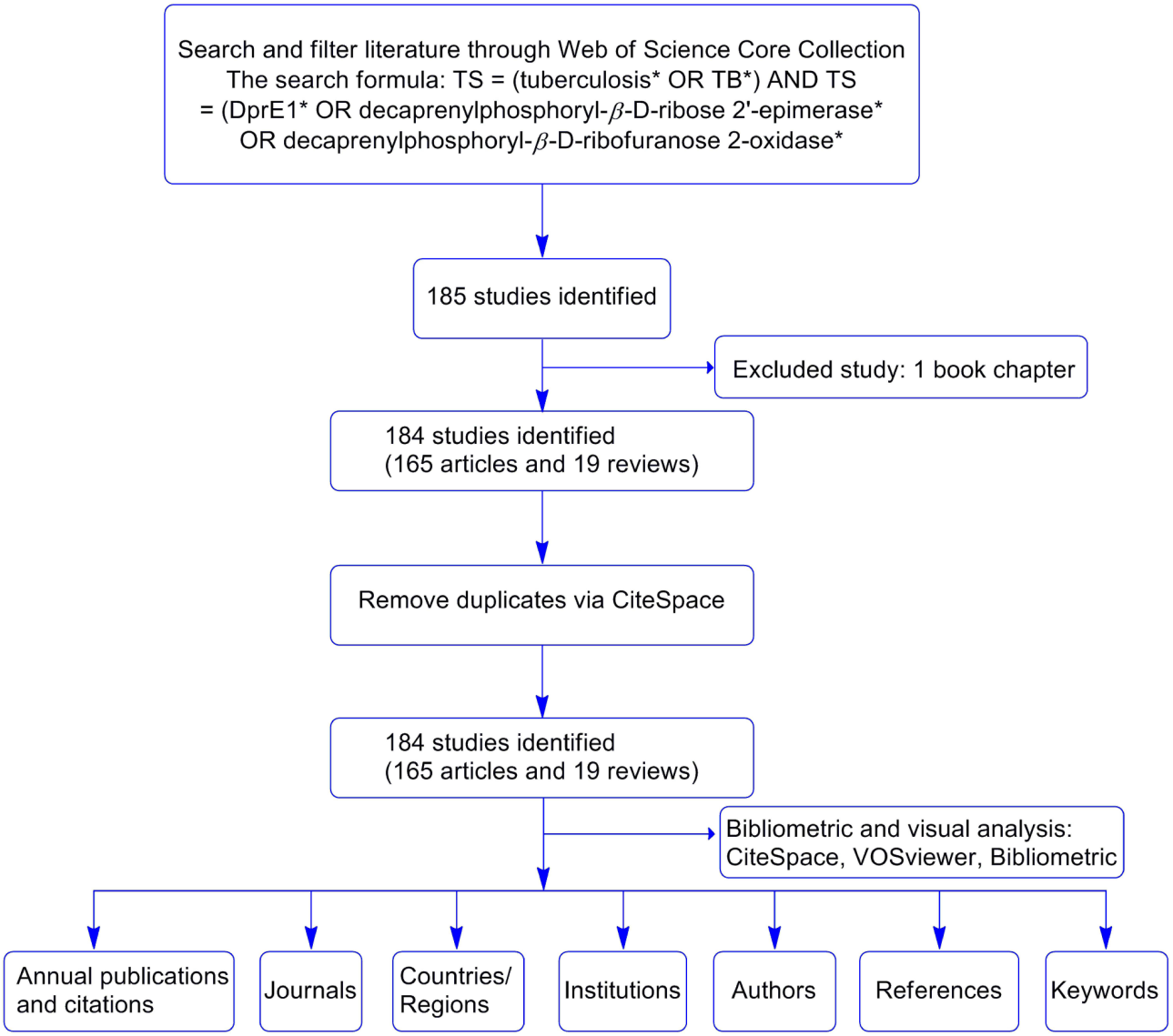


Figure 2 Flow diagram of data acquisition.

authors, institutions, countries, keywords or cited references.[31] The visualization maps were categorized into three types: network visualization map, density visualization map and overlay visualization map. Herein, VOSviewer was implemented to perform 1) a network of co-author, co-institution, and co-country analyses, 2) highly cited studies and co-cited references, and 3) keyword co-occurrence analysis. In this study, the visualization tool parameters were set to the defaults. Various visualization maps with distinct nodes, linkages, and colors convey diverse meanings. A comprehensive description of these maps is provided in the figure legends.

The CiteSpace software (version 6.3. R1) was developed by Professor Chaomei Chen. It is probably the most widely used technique to integrate bibliometric analysis with data mining methods for optimal visualization.[32,33] CiteSpace was employed in this investigation to implement an exhaustive examination of the keywords, references, authors, journals, institutions, and countries.[34] In this analysis, we established a time range from 2010 to 2024 and configured the time slice parameter to one year with the threshold was "k = 25". Utilizing the Pathfinder pruning algorithm, we performed a comprehensive and systematic analysis of various nodes, including keywords, cited references, authors, journals, institutions, and countries. The Pathfinder pruning method was selected to optimize the network structure. Top N = 50 was chosen as the selection criteria, with other attribute values set to default parameters. This threshold captures

a significant portion of the data while ensuring representation of the most influential authors in each time slice, striking a balance between comprehensiveness and clarity in our results.[35] The clusters of referenced citations were visualized via the LLR (log-likelihood ratio) strategy. Apart from this the aforementioned parameters, we also examined two additional significant parameters. The modularity (Q value) and mean silhouette scores (S value) were utilized in the cluster analysis to assess the overall structural characteristics of the network, with the cluster quality of the cluster map being satisfactory when $Q > 0.3$ and $S > 0.5$.[36] Additionally, burst analysis of keywords was used as a metric for the study's focus.[37]

The R-bibliometrix package (version 4.1.0) was developed by Professor Massimo Aria and Professor Corrado Cuccurullo. Herein, R-bibliometrix was utilised to undertake an exhaustive analysis of the authors, journals, nations, institutions, keywords and references.[38] The bibliometrics website (http://bibliometric.com/) was used to display the worldwide collaboration atlas.

Results

Annual Publications and Citations

Between 2010 and 2024, 176 articles, 20 reviews, and one letter were obtained from the WoSCC. All the studies received 3405 citations, resulting in an H-index of 33. The mean number of citations per item was 17.28, whereas the mean number of citations per year was 243.21. The annual number of publications on DprE1 in TB has increased over the last 15 years (Figure 3). The number of citations also increased rapidly, indicating an ascending trend with an increase in the annual output. Pearson's correlation analysis indicated a strong positive link between the number of publications and citations (Supplementary Figure 1), with a high Pearson's correlation coefficient ($r = 0.952$, $p < 0.005$).

Journal Analysis

Research in this field was mostly disseminated among 79 journals, with the productivity and average impact factors (IF) of the top nine active journals during the past few years, as shown in Table 1 (more than four publications). Most journals with a high reputation publish studies on the main aspects of medicinal chemistry. The European Journal of Medicinal Chemistry is a leading publication in this domain, with published 19 papers. The journal's average IF in the past five years is 6.1, with an IF of 6.0 in 2023, and it ranks in Q1 according to the JCR Quartile in 2023. The Journal of

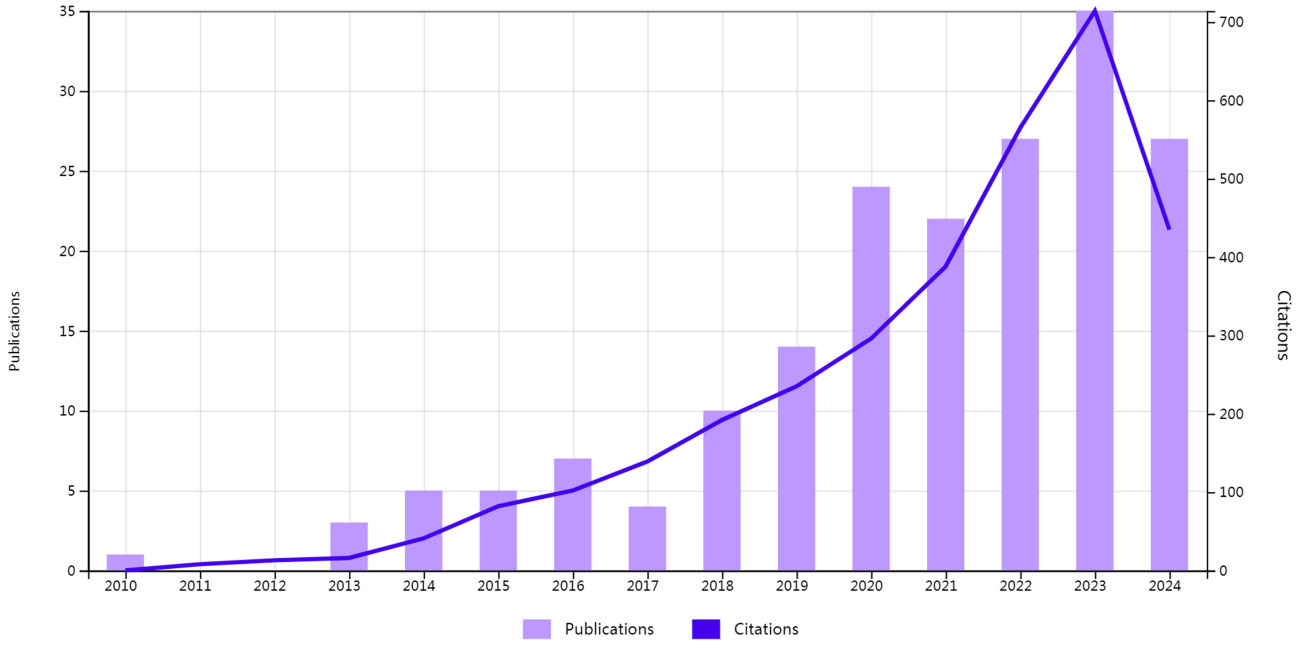


Figure 3 Annual number of publications and citations worldwide from 2010 to 2024.

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Table 1 Productivity and Impact Factors of Top 9 Active Journals

Ranking	Journals	Numbers	Total Citations	IF 2023	5 Years Impact Factor	JCR Quartile 2023
1	European Journal of Medicinal Chemistry	19	415	6.0	6.1	Q1
2	Journal of Medicinal Chemistry	17	674	6.8	7.1	Q1
3	ACS Medicinal Chemistry Letters	11	284	3.5	3.9	Q2
4	Bioorganic & Medicinal Chemistry Letters	10	364	2.5	2.4	Q3/Q2
5	Antimicrobial Agents and Chemotherapy	9	132	4.1	4.3	Q2/Q1
6	Journal of Molecular Structure	6	19	4.0	3.5	Q2
7	Journal of Biomolecular Structure and Dynamics	5	11	2.7	3.2	Q3/Q2
8	ChemistrySelect	4	38	1.9	1.9	Q3
9	ChemMedChem	4	45	3.6	3.5	Q2/Q2

Medicinal Chemistry is the second-ranked journal, comprising 17 published papers, with an average IF of 7.1 in the past 5 years, an IF of 6.8 in 2023 and JCR Quartile ranking of Q1 in 2023. Not surprisingly, these two journals published studies pertaining to a broad range of subjects of medicinal chemistry and were fascinated by medicinal chemists and pharmacologists.

Global Contribution of Countries, Institutions, Authors

Analysis of Countries/Regions

Sixty-five nations have published pertinent research. Figure 4A illustrates that India was first placed in publications with 74 (27.39%), followed by China with 32 (22.97%), and the USA with 31 (5.72%). These three nations account for approximately 56.08% of the total number of articles in this domain. Figure 4B illustrates that India (1526 citations), the USA (826 citations), and the UK (533 citations) are leading countries in terms of total citations. A total of 2297 collaborations were found within the global cooperation networks, five of which were India–UK (147 collaborations), India–USA (119 collaborations), India–China (102 collaborations), UK–China (85 collaborations), and USA–UK (81 collaborations) (Figure 4C).

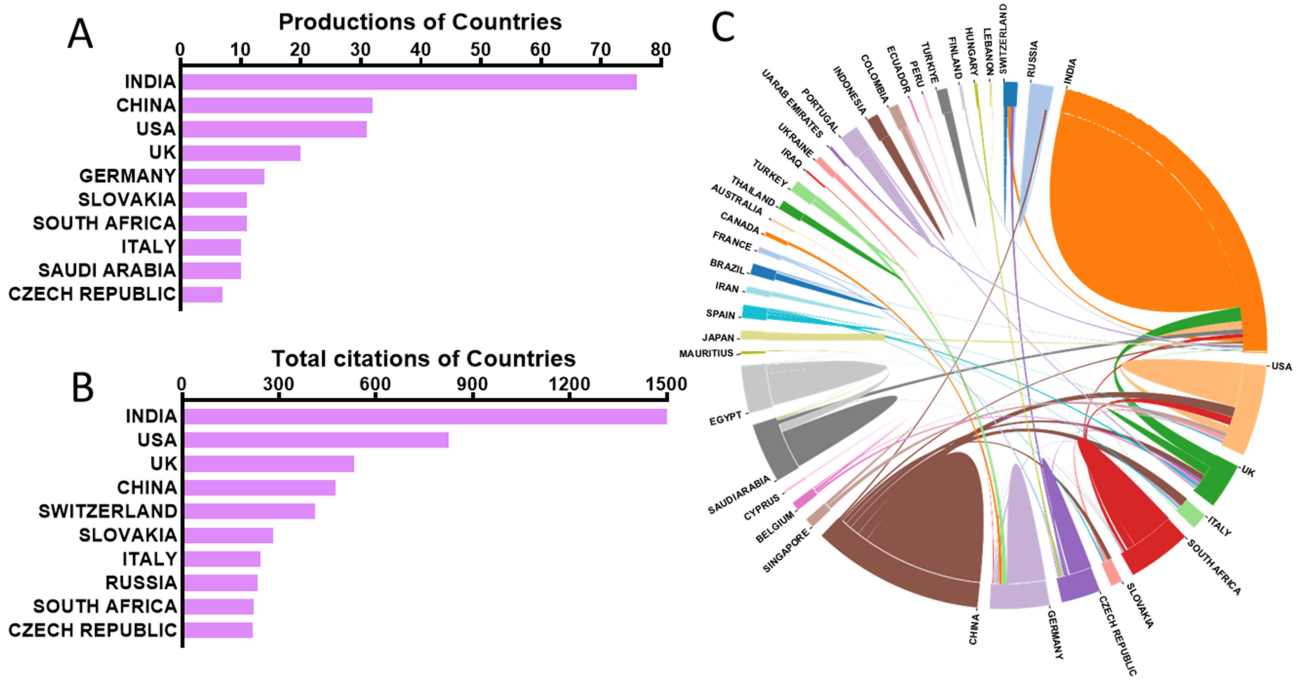

Figure 4 Contributions of countries. (**A**) The top ten countries in publications. (**B**) The top ten countries in total citations. (**C**) Cooperation networks of active countries.

Table 2 Top 11 Funding Agencies of DprE1 in TB

Rank	Funding Agencies	Record Count (%)
1	United States Department of Health Human Services	15 (7.58)
2	National Institutes of Health (NIH)	14 (7.07)
3	National Natural Science Foundation of China	12 (6.06)
4	Council of Scientific and Industrial Research (CSIR), India	10 (5.05)
5	Department of Science and Technology, India	9 (4.55)
6	Slovak Research and Development Agency	9 (4.55)
7	The University Grant Commission, India	9 (4.55)
8	Indian Council of Medical Research	8 (4.04)
9	National Mega-project for Innovative Drugs, China	8 (4.04)
10	European Union, EU	7 (3.54)
11	The National Institute of Allergy and Infectious Diseases (NIAID)	7 (3.54)

Analysis of Funding

Table 2 lists the distribution of the top 11 most frequent funding sources in this field, the main funding agencies were from the United States, India and China. America and India played an important role in supporting to research on DprE1 in TB with 36 projects, respectively. United States Department of Health Human Services, National Institutes of Health (NIH) and the National Institute of Allergy and Infectious Diseases (NIAID) were from the United States. Council of Scientific and Industrial Research (CSIR), the Department of Science and Technology, the University Grant Commission, and the Indian Council of Medical Research were from India. China launched 20 projects supported by two main funding agencies, the National Natural Science Foundation of China and the National Mega-project for Innovative Drugs.

Analysis of Institutions

According to VOSviewer, 352 institutions are dedicated to DprE1 in TB, and 8 institutions have published 7 or more articles (Table 3). The most prolific institutions were Capital Medical University (18 publications), followed by the Council of Scientific and Industrial Research (17 publications), the Chinese Academy of Medical Sciences & Peking Union Medical College (15 publications), Comenius University Bratislava (11 publications), the University of Pavia (10 publications), AstraZeneca (9 publications), the University of Cape Town (7 publications), and the University of Notre Dame (7 publications). According to the ranking, two Chinese institutions were listed in the top three in terms of publications. It is worth mentioning that the Chinese Academy of Medical Sciences and Peking Union Medical College is a single institution, although they were recognized as two institutions by WoSCC. Intriguingly, the most prolific institutions were academic institutions, except for AstraZeneca, a pharmaceutical company. The Swiss Federal Institute of Technology Domain took the lead in conducting studies in this field (Supplementary Table 1).

Table 3 The Top 8 Most Active Institutions

Ranking	Institution	Country	Numbers	Total Citations	Average Citations
1	Capital Medical University	China	18	279	15.50
2	Council of Scientific and Industrial Research	India	17	464	27.29
3	Chinese Academy of Medical Sciences & Peking Union Medical College	China	15	243	16.20
4	Comenius University Bratislava	Slovakia	11	288	26.18
5	University of Pavia	Italy	10	246	24.60
6	AstraZeneca	Sweden	9	484	53.78
7	University of Cape Town	South Africa	7	67	9.57
8	University of Notre Dame	USA	7	261	37.29

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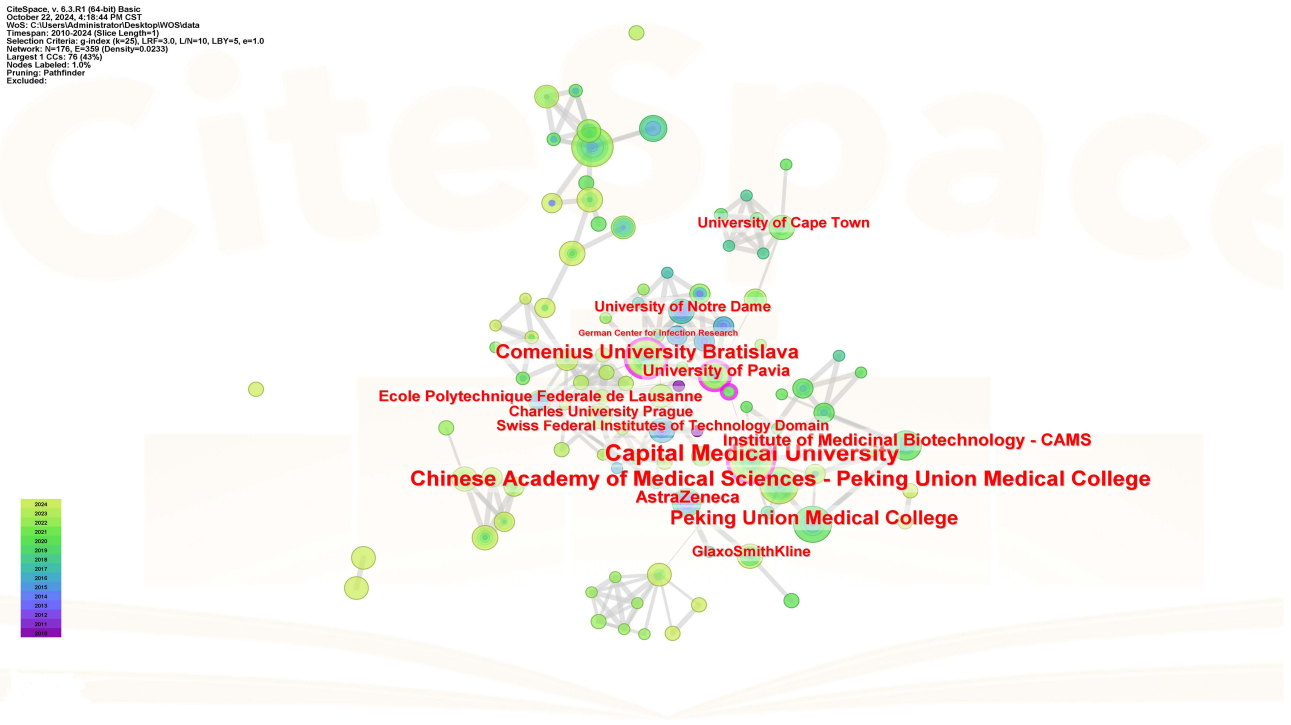

Figure 5 Contributions of institutions.

Furthermore, a network of institutional analyses was established, including 176 nodes and 359 links, via Citespace (Figure 5). The figure illustrates the institution as circles and the extent of collaboration as lines, with varying thicknesses indicating different collaboration levels. Notable academic partnerships were identified among four universities in China, Slovakia, and Italy: Capital Medical University, Chinese Academy of Medical Sciences and Peking Union Medical College, Comenius University Bratislava, and University of Pavia. Among them, two Chinese institutions had a very close cooperative relationship, 15 times.

Analysis of Authors

A total of 1104 authors published pertinent papers, and Table 4 lists the 11 most prolific authors. Yu Lu and Bin Wang (Capital Medical University, China) were the most influential authors with 18 publications, respectively, followed by

Table 4 The Top 11 Most Productive Authors

Ranking	Author	Institution	Country	Numbers	Total Citations	H-Index
1	Yu Lu	Capital Medical University	China	18	266	9
2	Bin Wang	Capital Medical University	China	18	270	9
3	Laurent R. Chiarelli	University of Pavia	Italy	10	246	7
4	Kai Lv	Chinese Academy of Medical Sciences & Peking Union Medical College	China	8	143	5
5	Katarína Mikušová	Comenius University in Bratislava	Slovakia	8	273	6
6	Vijay M. Khedkar	Council of Scientific and Industrial Research	India	7	221	7
7	Mingliang Liu	Chinese Academy of Medical Sciences & Peking Union Medical College	China	7	142	6
8	Marvin J. Miller	University of Notre Dame	USA	7	261	6
9	Vasan K Sambandamurthy	AstraZeneca	Sweden	7	447	7
10	Dhiman Sarkar	Council of Scientific and Industrial Research	India	7	221	7
11	Sreevalli Sharma	AstraZeneca	Sweden	7	316	6

Laurent R. Chiarelli (University of Pavia, Italy), Kai Lv (Chinese Academy of Medical Sciences & Peking Union Medical College, China) and Katarína Mikušová (Comenius University in Bratislava, Slovakia) with more than 8 publications.

Co-Authorship, Co-Institution, and Co-Country Analysis

A clustering map of the collaboration network among authors, institutions, and countries in the field of DprE1 in TB is shown in Figure 6. Typically, the nodes in the figures denote the authors, institutions, or countries. The number of published articles increased with node size. Collaborative interaction between nodes is exemplified by the connections between them. In automated mode, the nodes, lines, and cluster outlines were categorized by year. Red indicates a relatively recent age, and blue indicates a distant age.

Figure 6A shows the 38 authors with more than four collaborations. The nodes of Yu Lu and Bin Wang were the largest and cooperated closely with other authors. It is worth mentioning that Yu Lu and Bin Wang were term members of the Beijing Chest Hospital affiliated with the Capital Medical University. They founded a solid collaboration with Chinese researchers and had a good relationship with Laurent R. Chiarelli (Italy), Giovanni Stelitano (Italy), and Katarína Mikušová (Slovakia). The clustered network of co-authorship analysis showed that authors with collaborations can be divided into three consensus sets: American, European, and Chinese researchers.

Figure 6B shows the co-institution from 59 institutions with more than three collaborations. Figure 6C shows the co-country from 18 countries with more than three collaborations. India was the most active nation, with 27 collaborations with other countries, such as the UK, the USA, China, and Switzerland. The UK, with ten authors, cooperated with India.

Highly Cited Studies and Co-Cited References

VOSviewer was used to generate a network visualization map for document citation analysis. Figure 7 shows that the citation frequency is inversely proportional to the magnitude of the node. The most frequently referenced study was conducted by Trefzer et al and was published in the Journal of the American Chemical Society. Furthermore, we summarize the fundamental information of the ten most frequently referenced papers in this field in Table 5. Reference analysis is a critical component of bibliometrics. All references were categorized into 11 primary sub-clusters, as illustrated in Supplementary Figure 2, and co-cited references were citations that occurred concurrently with other texts. The silhouette values of these clusters surpassed 0.9031 with an average of 0.8039, signifying their robust homogeneity.

References Burst Analysis

To gain a more profound understanding of the developmental trajectory of DprE1 in TB research in recent years, references exhibiting significant citation bursts were identified using CiteSpace. Figure 8 presents the top 20 references, including their frequency, authors, publishing journals, years, and the most significant citation bursts. The concept of reference with citation burst initially appeared in 2009, as noted by Makarov V (doi: 10.1126/science.1171583).[11] The research conducted by Makarov V (doi: 10.1002/emmm.201303575) demonstrated the highest burst strength of 9.6.[39]

Keywords Co-Occurrence Analysis

Figure 9A presents a density visualization map of the terms. Following manual consolidation of synonymous terms, 28 keywords, each with at least 10 occurrences, were derived from the original set of 794 keywords. Among these, the top 10 most common terms with the greatest occurrence frequencies were as follows: “dpre1” (88), “tuberculosis” (68), “mycobacterium-tuberculosis” (50), “benzothiazinones” (44), “inhibitors” (41), “derivatives” (38), “identification” (37), “design” (35), “kill mycobacterium-tuberculosis” (34), and “molecular docking” (34). An overlay visualization map of these keywords is shown in Figure 9B.

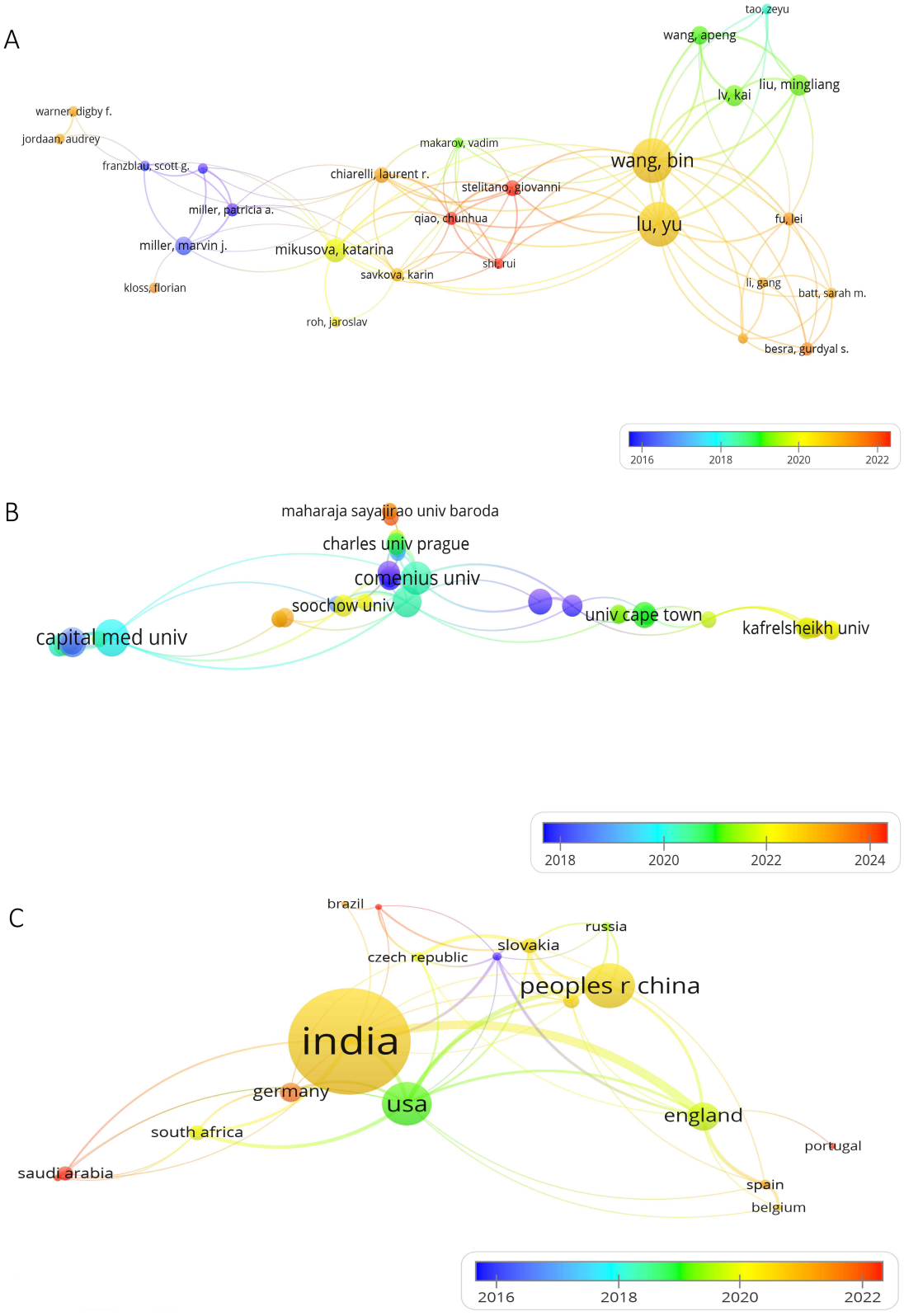

Figure 6 Clustered network of co-authorship analysis on DprE1 in TB. (**A**) Co-authorship analysis of authors. (**B**) Co-authorship analysis of institutions. (**C**) Co-authorship analysis of countries.

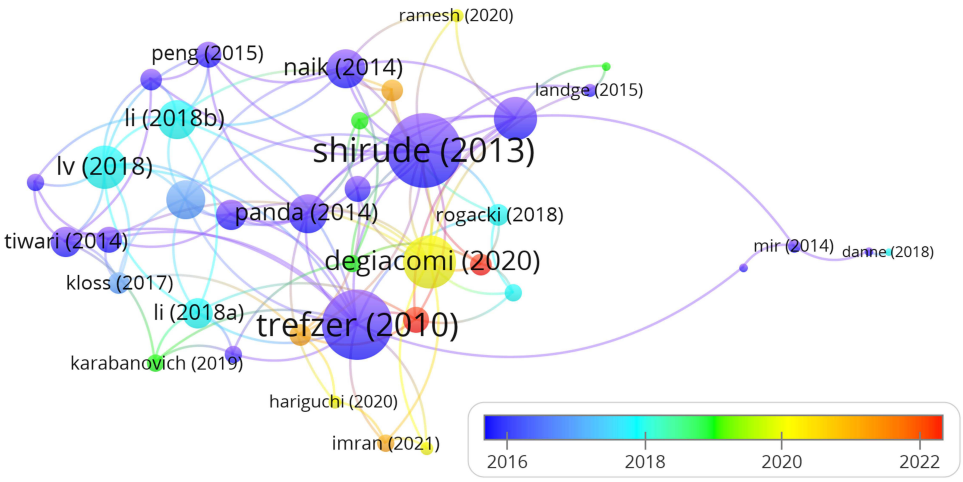

Figure 7 Network visualization map of document citation analysis generated by VOSviewer. The node size was proportional to the citation times.

Keywords Burst Analysis

Herein, we employed a burst detection algorithm to extract keywords from publications linked to DprE1 in the TB. Twenty keyword phrases that demonstrated the most significant citation bursts emerged (Figure 10). Of them, "resistance", "inhibition" and "arabinofuranose" were the top 3 keywords with the strongest burst strength (3.23, 2.76, and 2.41, respectively). Remarkably, the citation burst time of these keywords including "drug resistance" (2022–2024), "noncovalent inhibitors" (2022–2024) and "molecular dynamics" (2023–2024) has continued to 2024 and the bursts are keeping going.

Figure 11 illustrates the migration and evolution of the ten primary research avenues and the substance of the research hotspots over time. The greater the number, the fewer were the keywords included. They were "dpre1 inhibitor",

Table 5 Top 10 highly Cited Studies in the Field of DprE1 in TB

Ranking	Title	Citations	Journal	First Author	Year-Published
1	Benzothiazinones: Prodrugs that covalently modify the decaprenylphosphoryl-β-D-ribose 2′-epimerase DprE1 of *Mycobacterium tuberculosis*	178	Journal of American Chemical Society	Trefzer C.	2010
2	Azaindoles: Noncovalent DprE1 inhibitors from scaffold morphing efforts, kill *Mycobacterium tuberculosis* and are efficacious in vivo	132	Journal of Medicinal Chemistry	Shirude P. S.	2013
3	Sulfur rich 2-mercaptobenzothiazole and 1,2,3-triazole conjugates as novel antitubercular agents	94	European Journal of Medicinal Chemistry	Mir F.	2014
4	Development of selective DprE1 inhibitors: Design, synthesis, crystal structure and antitubercular activity of benzothiazolylpyrimidine-5-carboxamides	91	European Journal of Medicinal Chemistry	Chikhale R.	2015
5	Development of 3,5-dinitrobenzylsulfanyl-1,3,4-oxadiazoles and thiadiazoles as selective antitubercular agents active against replicating and nonreplicating *Mycobacterium tuberculosis*	90	Journal of Medicinal Chemistry	Karabanovich G.	2016
6	Synthesis and bioactivity of novel triazole incorporated benzothiazinone derivatives as antitubercular and antioxidant agent	87	European Journal of Medicinal Chemistry	Shaikh M. H.	2016
7	Discovery of pyrazolopyridones as a novel class of noncovalent DprE1 inhibitor with potent anti-mycobacterial activity	80	Journal of Medicinal Chemistry	Panda M.	2014
8	4-Aminoquinolone piperidine amides: Noncovalent inhibitors of DprE1 with long residence time and potent antimycobacterial activity	76	Journal of Medicinal Chemistry	Naik M.	2014
9	Synthesis and biological evaluation of novel 1,2,3-triazole derivatives as anti-tubercular agents	72	Bioorganic & Medicinal Chemistry Letters	Ali A. A.	2017
10	Thiolates chemically induce redox activation of BTZ043 and related potent nitroaromatic anti-tuberculosis agents	70	Journal of American Chemical Society	Tiwari R.	2013

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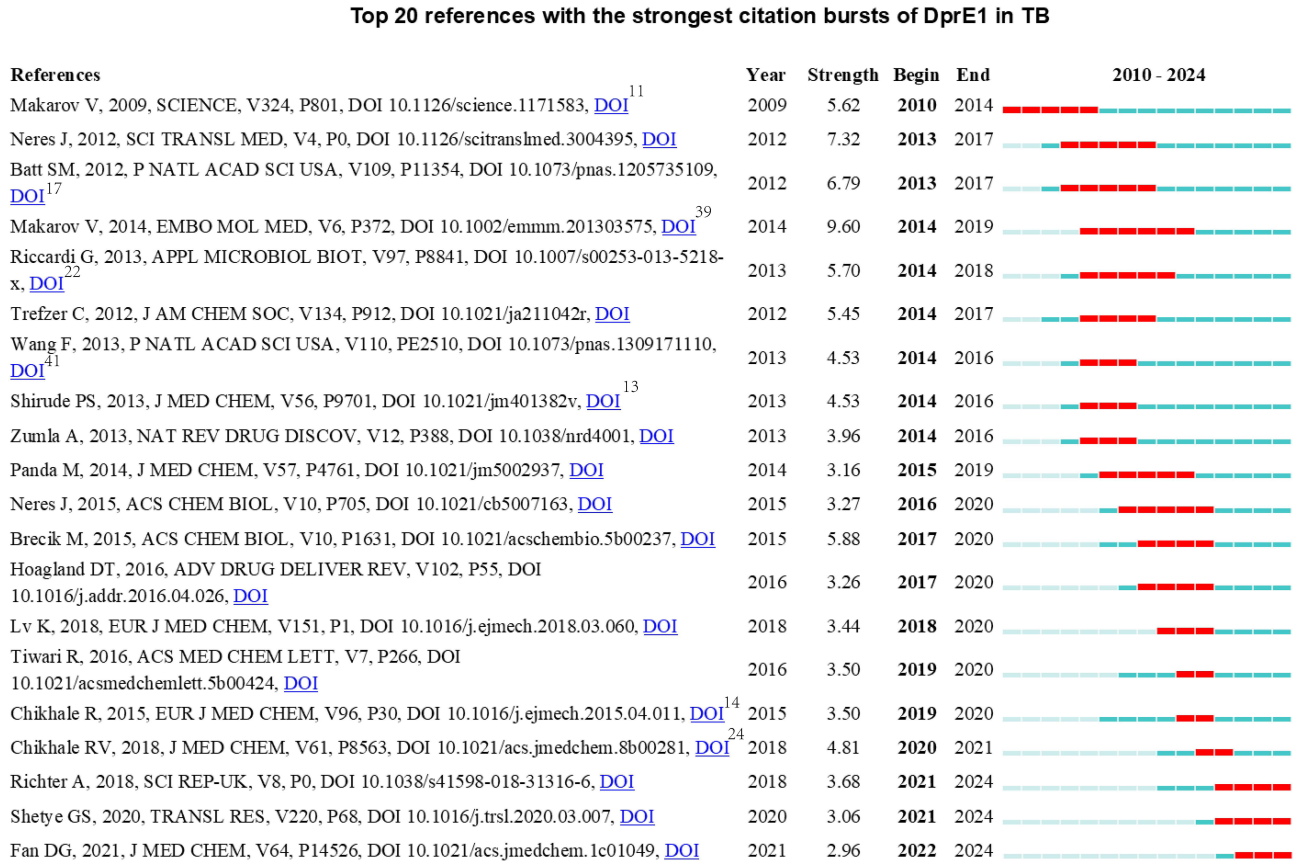

Figure 8 Top 20 references with the strongest citation bursts of DprE1 in TB.

"pharmacokinetic benzothiazinone derivative", "tb drug discovery efforts", "potential anti-tuberculosis agent", "papain-like proteinase", "cellular envelope", "enzyme target", "synthesis structural characterization", "potent nitroaromatic anti-tuberculosis agent" and "silico investigation." Noticeably, "dpre1 inhibitor" was the richest category of articles, due to it was the most representative term in this field, which not only have a large number of articles but also have new research content every year from 2010 to 2024.

Discussion

General Description

In this study, 184 publications on DprE1 in TB published in the WoSCC database from 2010 to 2024 were examined using VOSviewer 1.6.20 and CiteSpace 6.3. R1 and R-bibliometrix 4.1.0. The main conclusions were obtained from the following sources: contribution of journals, countries, funding, institutions, authors, time distribution, space-time distribution, hotspots, frontiers, and so on.

The number of published articles increased from 2013 to 2024. After 2018, the number of published articles was maintained at more than ten, indicating a good development trend in this field. As Figure 2 shows, surprisingly, there were no published articles related with DprE1 in 2011 and 2012 according to WoSCC, in deed, there were some articles can be retrieved from MEDLINE database, such as "Trefzer C (doi: 10.1021/ja211042r)", "Batt S. M. (10.1073/pnas.1205735109)" and "Crellin P. K. (10.1371/journal.pone.0016869)".

Researchers from Russia (Makarov, V.) and Switzerland (Cole, S. T.) pioneered this field, creating a milestone. At the same time, the United States and Europe had higher centrality, indicating that academic cooperation was a higher priority for researchers in these two regions in the initial stage. India ranked first in terms of the number of published papers and

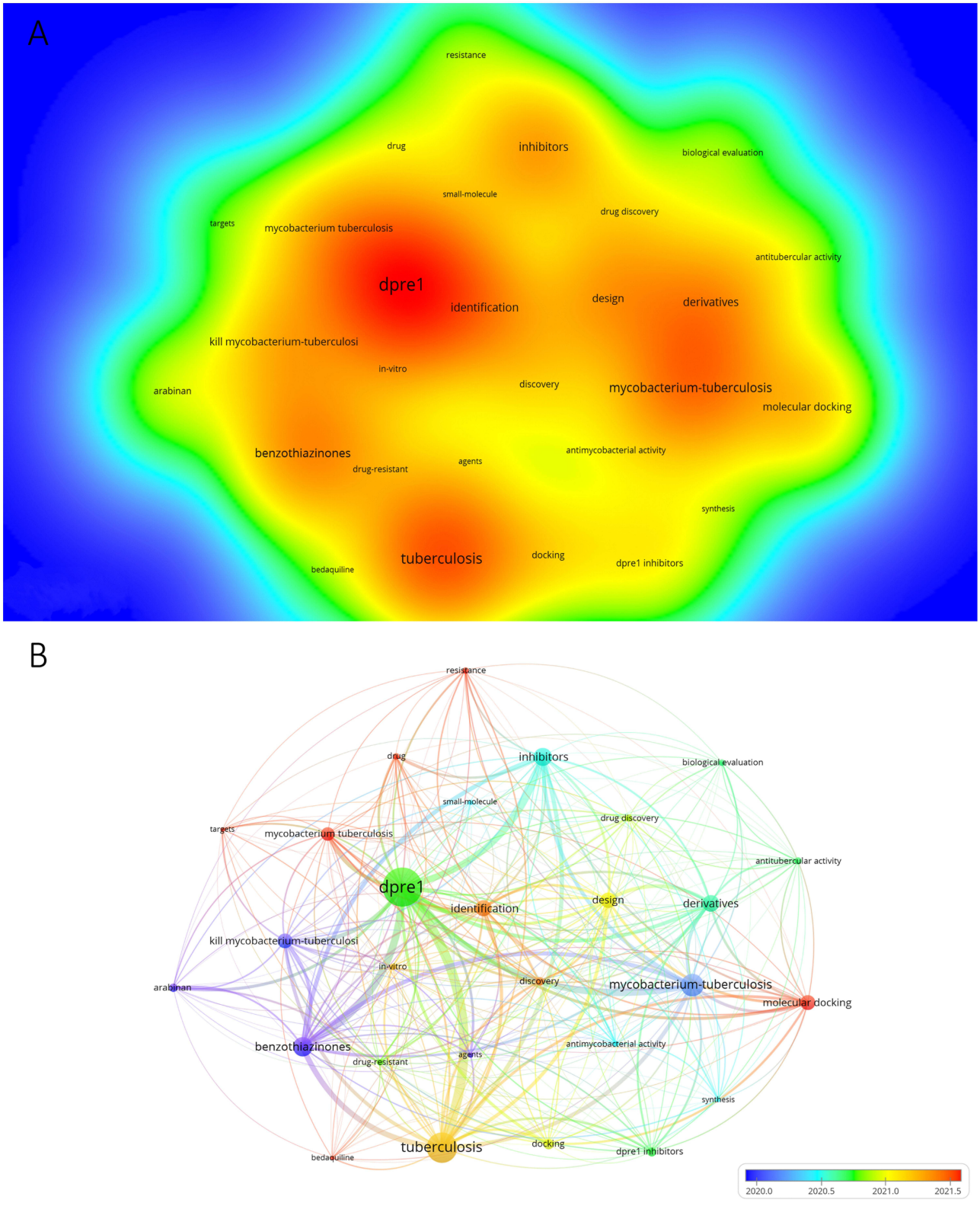

Figure 9 (**A**) Keyword co-occurrence analysis by VOSviewer. The deeper the color, the higher the co-occurrence frequency of keywords. (**B**) Overlay visualization map of keyword co-occurrence analysis by VOSviewer. Each node represented a keyword. The node size was proportional to the occurrence frequencies.

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Top 20 Keywords with the strongest citation bursts of DprE1 in TB

Keywords	Year	Strength	Begin	End	2010 - 2024
drugs	2014	2.35	**2014**	2018	
accurate docking	2014	1.87	**2014**	2016	
antitubercular agents	2016	2.35	**2016**	2018	
dpre1	2014	1.46	**2016**	2018	
resistant *mycobacterium tuberculosis*	2017	1.76	**2017**	2018	
inhibitors	2015	1.46	**2017**	2017	
derivatives	2014	1.41	**2018**	2018	
small molecule	2019	2.04	**2019**	2020	
dpre1 enzyme	2020	2.01	**2020**	2021	
arabinofuranose	2021	2.41	**2021**	2022	
inhibition	2022	2.76	**2022**	2022	
target	2022	2.12	**2022**	2024	
tuberculosis	2022	2.12	**2022**	2024	
antitubercular evaluation	2018	1.63	**2022**	2022	
drug resistance	2022	1.52	**2022**	2024	
noncovalent inhibitors	2022	1.52	**2022**	2024	
benzothiazinone derivatives	2022	1.52	**2022**	2024	
resistance	2018	3.23	**2023**	2024	
in vitro	2016	2.13	**2023**	2024	
molecular dynamics	2023	1.49	**2023**	2024	

Figure 10 Top 20 Keywords with the strongest citation bursts of DprE1 in TB.

Figure 11 The timeline of keywords. Each period corresponds to a longitudinal time axis, and the keywords on the time axis represent the first appearance of the keywords in this period. The node size represents the total frequency of this keyword for several years. The annual ring of node content, the color of each layer represents the year when the keyword reappears, and the thickness is the frequency of this year; Connecting means co-occurrence.

centrality. China ranked second in the number of papers published, but fourth in centrality, which may be ascribed to its late start. Asia has the largest number of papers published, followed by Europe.

Among the top ten institutions with the highest production, two had a considerable number of publications from China. The Capital Medical University had the greatest centrality (0.17), indicating its substantial cooperation potential and academic influence.

Yu Lu and Bin Wang, from China, were the most prolific authors in this discipline and were affiliated with the Capital Medical University. The H-index was 9 in this field, which shows that it significantly influenced the research field. Based on an examination of published articles, most of the highly cited studies were dedicated to the development of DprE1 inhibitors to eradicate TB.

IF is a conventional metric for evaluating journal quality. Our findings indicate that among the top nine journals in productivity, the "Journal of Medicinal Chemistry" possessed the highest IF of 6.8, with 17 published articles receiving 674 citations, signifying the high quality and peer recognition of these publications in the field. The "European Journal of Medicinal Chemistry" and the "Journal of Medicinal Chemistry" have been acknowledged as high-impact journals in the domain of pharmacy.

The Main Research Directions and Focuses Currently

The keyword refers to the authors' refinement and summarization of the article's content, thereby reflecting the main ideas of the article. The keyword burst detection can discern research focal points and prospective development trends in this field. Based on keyword analysis, the direction of the efforts to develop DprE1 inhibitors in the last 15 years was straightforward, that is, the historical evolution is not only DprE1 but also TB, as follows.

DprE1 has been identified as a highly druggable target for controlling mycobacterial growth and was identified as a new class of antitubercular agents in 2009,[11] showing the capability of offering potential drug candidates and paving the way for further pharmacological studies on both MDR- and XDR-TB treatment. Within a brief timeframe, the BTZ scaffold has garnered significant interest from scientists and researchers globally in the realm of antimycobacterials, owing to the lead compound BTZ043 demonstrating remarkably potent in vitro and ex vivo minimal inhibitory concentrations (MIC) in the nanomolar range. Inspired by this study, the PBTZ family was developed sooner and displayed higher potency, safety, and efficacy in vitro and in vivo than the parent BTZ043.[39]

In addition to benzothiazinones, several scaffolds that have shown effectiveness include nitrobenzamides, azaindoles, pyrazolopyridines, triazoles, quinoxalines, benzothiazoles, thiadiazoles, aminoquinolines, and their derivatives, which have been shown to be active against Mtb. Comprehensive endeavors have been made to uncover several scaffolds that exhibit strong binding affinity to the target while maintaining improved pharmacokinetic qualities to deliver sufficient quantities to the target, rather than to host proteins.

So far, anti-TB drug research efforts have mostly focused on discovering medications that target the actively replicating form of Mtb; nevertheless, it is equally essential to identify innovative treatments capable of inhibiting and eradicating the latent or dormant form.[40,41] Significant progress has been achieved in identifying novel medications for the treatment of drug-susceptible, MDR-, and XDR-TB during the last decade, and new combination regimens are being developed and evaluated in clinical trials to address TB resistance.

To date, DprE1 inhibitors with antimycobacterial activity have been developed mainly using synthetic chemistry or computer-aided design strategies. These inhibitors are sorted into two categories, depending on the mechanism of DprE1 inactivation. One family is known to inhibit DprE1 irreversibly by framing a covalent adduct with cysteine 387 in the active site of DprE1, whereas the others act as competitive noncovalent inhibitors. Coincidentally, BTZ043 and PBTZ169 are identified as the most promising covalent inhibitors, whereas TBA-7371 and OPC-167832 represent the most notable noncovalent inhibitors. According to the pharmacokinetic study, PBTZ169 (TD_{50} = 58 μg/mL) was found to be less toxic than BTZ043 (TD_{50} = 5 μg/mL) using the HepG2 human cell line.[39] Furthermore, OPC-167832, characterized by its superior kinetic properties, is considered to possess significant therapeutic potential. Research on inhibitors targeting DprE1 through different mechanisms is showing a closely contested competitive situation. However, although the existing DprE1 inhibitors have shown good anti-TB effects, there are still potential challenges of drug resistance. In covalent inhibitors such as benzothiazinones, drug resistance mainly occurs due to mutations where the

cysteine 387 residue, which covalently binds to the inhibitor in the DprE1 active site, is replaced by serine or glycine. Additionally, in noncovalent inhibitors, mutations in Tyr314 and Trp314 residues, which form van der Waals forces with DprE1, may also lead to drug resistance.[13,42] Overall, covalent inhibitors are mostly nitro derivatives and often carry the risk of mutagenicity. Noncovalent inhibitors may provide a safer option; nevertheless, their anti-TB efficacy is often less pronounced.

In recent years, the emergence of technologies such as artificial intelligence (AI) and computer-aided drug design (CADD) has revitalised the study and development of DprE1 inhibitors.[26] These new technologies are mainly applied in identifying promising candidates and optimizing DprE1 inhibitors. CADD mainly adopts two strategies: ligand-based drug design (LBDD) and structure-based drug design (SBDD). Given the increasingly abundant data on DprE1 currently available, SBDD has demonstrated greater potential in the discovery of DprE1 inhibitors. Currently, techniques such as molecular docking and structure-based pharmacophore modeling in SBDD strategies have been applied to the research of DprE1 inhibitors. Q-SAR models in LBDD are typically used for the optimization of DprE1 inhibitors for enhanced efficacy. Machine learning (ML) is further beneficial for the creation and optimization of DprE1 inhibitors. The application of these new technologies not only accelerates the discovery of DprE1 inhibitors with novel scaffold but also enhances their biological efficacy and drug-like properties.[43]

Natural products play a vital role in the drug discovery and development process.[44,45] Gupta et al summarized 23 plant species have been identified as containing active compounds effective against MDR-TB retrieved from 86 research articles (published from 1994 to 2016).[46] Nevertheless, there are few DprE1 inhibitors inspired from natural product have been reported to date. Baptista et al reported tiliacorine (−12.7 kcal/mol), nortiliacorinine (−10.9 kcal/mol), and 13′-bromotiliacorine (−10.3 kcal/mol), which are derived from *Tabernaemontana elegans* Stapf. or *Tiliacora triandra*, exhibit lower binding energies with DprE1 than BTZ043 (−10.1 kcal/mol) via molecular reverse docking approach. This result suggests that these compounds of natural origin are likely to be inhibitors of DprE1.[47] In our previous study, we serendipitously discovered that natural compound rosmarinic acid (RA) exhibited moderate inhibitory activity against UDP-galactopyranose mutase from Mtb with interesting binding affinity value.[48–50] Encouraged by these results, we continue to conduct a large-scale screening campaign against DprE1, and research is now underway in the laboratory to investigate this possibility.

In our research, CiteSpace, VOSviewer and bibliometrics tools were adopted to conduct a systematic analysis of the literature on DprE1 in TB. The analysis covers multiple indicators including publications, citations, journals, countries, funding, institutions, authors, co-author, co-institution, co-country, highly cited studies, co-cites references, references burst, keyword co-occurrence, keyword clustering, and keywords burst. The research results not only reflected the sustained-growth publications in this field but also highlight that researchers have established robust and extensive collaborative relationships through co-authorship networks, institutional collaborations, and international partnerships. Most importantly, through references burst analysis and keywords burst analysis, the current research trends and hotspots in the DprE1 field have been elucidated. Specifically, from 2010 to 2024, the number of publications in this domain has exhibited a sustained upward trend. This result indicates that substantial progress has been achieved on DprE1 in TB since DprE1 discovered. Furthermore, among these findings, the majority of highly cited studies have concentrated on the development of DprE1 inhibitors for TB treatment. Notably, four DprE1 inhibitors (BTZ-043, Macozinone, TBA-7371, and OPC-167832; Table 6) are now in Phase II clinical trial. In

Table 6 DprE1 Inhibitors in Clinical Trials

Inhibitor's Name	Scaffold	Research Institute	Phase
BTZ-043	Benzothiazinone	Hans-Knoell-Institute for Natural Products Research	II
Macozinone	Benzothiazinone	The Swiss Federal Institute of Technology in Lausanne and Nearmedic Plus	II
TBA-7371,	Azaindole	AstraZeneca and TB Alliance	II
OPC-167832	3,4-Dihydrocarbostyril	Otsuka Pharmaceutical Co., Ltd.	II

addition, the molecular modeling study conducted by the Parkesh group indicated that DprE1 and DprE2 interact in the disordered region, which may affect ligand binding and therapeutic efficacy, thus posing an additional challenge for the development of new clinical compounds.[51,52]

DprE1 has proven to be a highly promising anti-TB drug target; more importantly, it is not found in mammals; therefore, it is considered an ideal target for the treatment of TB. Through bibliometric analysis, we have identified valuable information such as the current research trends, hotspots, leading countries, institutions, and researchers in DprE1, providing valuable insights into in this field.

Restrictions

The relationship between DprE1 and TB was examined systematically in this study. However, certain constraints must also be considered. Initially, we considered only papers written in English; hence, the results published in other languages were excluded. Secondly, WoSCC is the most prevalent database with a huge amount of information and widely used for bibliometric analysis, the data used in this study only from WoSCC, the consequence was that the milestone studies of DprE1 in TB were excluded from this study, due to no records in WoSCC. Another database is also a crucial tool for medical readers, the MEDLINE database offers reliable medical information on the healthcare system, medicine, nursing, pre-clinical sciences, etc., serving as a distributor of medical goods.[53,54] In addition, a multitude of patents regarding DprE1 inhibitors has been launched; consequently, they were not included in this study. Third, we acquired only published literature from 2010 to 2024, resulting in the exclusion of the current research from the study.

Conclusion

In summary, America, Europe, and Asian countries have maintained a preeminent status in the DprE1 domain in TB. In recent years, research has focused on the development of DprE1 inhibitors to eradicate TB, including synthetic chemistry, in silico design, and molecular dynamics (MD) simulations.

Encouraged by BTZ043, PBTZ169, TBA-7371, and OPC-167832, which are currently being evaluated in clinical trials, more attention has been focused on their derivatives and their *in viro* and in vivo antitubercular activity.[55–58] Moreover, with the increase in anti-TB drug resistance, more articles associated with the treatment of drug-resistant Mtb clinical isolates will be published in the future. Moreover, profound collaboration across nations or institutions is necessary, and it is imperative to adopt an innovative cross-disciplinary approach to accelerate anti-TB drug development, such as AI/ML/DL approaches.[59,60] So far, there have been no reports on DprE1 inhibitors derived from natural products, which indicates that this field might be a promising research direction. This study reflects the development of DprE1 in TB from the perspective of bibliometrics and provides blueprint and specific guidance for scholars, especially, academic institution and pharmaceutical company could learn from these data to optimize research directions, enhance cooperation, and accelerate the development of DprE1 inhibitors, fighting against TB. Even, we hope that our findings would appeal researchers to pay more attention to address the challenges of TB, eradicating TB by 2035.

Data Sharing Statement

All the data are available from the corresponding authors upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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