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Mapping the Landscape of Recent Studies on Pyrimidine Derivatives as Antimicrobial Agents: A Bibliometric Analysis

Abduljalil Nesar[1], Muhammad Aman Azad[1], Roshaan Raihan[2], Azimullah Wafa[2], Ahmad Tamim Ghafari[3]

1. Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Kabul University
2. Department of Pharmaceutics, Faculty of Pharmacy, Kabul University
3. Department of Pharmacology, Faculty of Pharmacy, Kabul University

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*Corresponding Author:
Ahmad Tamim Ghafari
Address: Department of Pharmacology, Faculty of Pharmacy, Kabul University

Tamim.ghafari@yahoo.com

ABSTRACT

Background: Microbial resistance to various drugs is a significant challenge in treating infectious diseases, necessitating the development of new drugs. Pyrimidine, with diverse biological effects, is an effective component in antimicrobial drugs. Despite significant progress over the last decade in studying pyrimidine as an antimicrobial agent, a bibliometric analysis in this area is lacking. This analysis aims to fill that gap and provide insights into the field's evolution.

Methods: A comprehensive examination of the available literature published between 2015 and 2023 on pyrimidine derivatives as antimicrobial agents was done across the Scopus database. Microsoft Excel 365 was employed to analyze the quantitative variables, such as publications and citation counts, for the authors, institutions, countries, and journals. Furthermore, the network visualization and analysis of co-authorship, co-occurrence, and co-citation among countries, institutions, authors, and keywords were facilitated by VOSviewer.

Results: A total of 934 articles were selected for the study. The years 2019 and 2022 exhibited the highest volume of published papers on pyrimidine derivatives as antimicrobial agents between 2015 and 2023, with 125 publications each. A total of 53 countries contributed to the topic, with India leading in publications, followed by Egypt, China, Saudi Arabia, and the United States. Among journals, the Journal of Heterocyclic Chemistry had the highest number of publications (n = 50), followed by the European Journal of Medicinal Chemistry with 37 publications.

Conclusion: The findings offer crucial insights for researchers in choosing specific compounds for future studies, highlighting the importance of bibliometric analysis in advancing pyrimidine antimicrobial research.

Kewwors: Pyrimidine, Antimicrobial agents, Bibliographic Analysis

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1. Introduction

Infections caused by multidrug-resistant bacteria have become a significant contributor to global mortality (1). Tackling the growing threat of bacterial resistance requires continuous exploration of new antimicrobial compounds and careful use of antibacterial medications with diverse chemical structures and mechanisms (2). Currently, pioneering discoveries in antibacterial drugs focus on compounds containing pyrimidine. Pyrimidine, similar to pyridine, is an aromatic heterocyclic organic molecule (3,4). The term 'pyrimidine' was coined by Pinner, who combined 'pyridine' and 'amidine' to create the name (5). Pyrimidine, one of the three diazines, has nitrogen atoms at the 1 and 3 positions within its six-membered heterocyclic ring (3, 6).

Pyrimidine-based compounds exhibit a wide range of biological effects, showcasing their versatility in medicinal applications. These effects include anticancer and antiviral activities (4,7), efficacy against human immunodeficiency virus (HIV) (4,8–10), anti-inflammatory properties (11), antifungal attributes (7), and antibacterial activity (1,2,12,13). Additionally, these compounds demonstrate antioxidant (12, 13) and antihypertensive (14) properties, highlighting their potential as multifaceted therapeutic agents.

Many natural substances and their derivatives featuring the pyrimidine ring system have been identified, including nucleotides, thiamine (vitamin B1) (15), and alloxan. The pyrimidine ring is also present in various synthetic compounds, such as barbiturates and anti-HIV medications like zidovudine (16, 17). The positive biological activities and diverse modes of action of pyrimidine-containing heterocyclic compounds have garnered significant interest among scientists. The pyrimidine structure is crucial for numerous endogenous substances, facilitating interactions with genetic materials, enzymes, and other biopolymers within the cell (1). The presence of the pyrimidine ring in the thymine, cytosine, and uracil bases of both ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) further underscores its importance (4).

Researchers have made substantial efforts to discover and optimize the structures of pyrimidine derivatives, resulting in the identification of many novel compounds with promising profiles. Despite the extensive research on topics like antimicrobials, compiling a comprehensive review with relevant data can be challenging. Bibliometric analysis is a valuable tool for scientific mapping, providing a macroscopic overview of subjects such as antibiotics, emerging contaminants, antivirals, multidrug-resistant fungi, and antimicrobials (18). In the context of antimicrobial treatment, numerous reviews and studies on pyrimidine as an antimicrobial agent exist. Thus, employing quantitative data analysis, the bibliometric method allows for the investigation, assessment, and examination of extensive scientific data (19). Recognized as a comprehensive approach, bibliometric analysis helps identify trends, gaps, social networks, intellectual organization, and cognitive structure within a specific research subject (19, 20). This method reveals the evolutionary subtleties of a particular field while highlighting emerging areas (20). Therefore, this study aims to identify and analyze research trends related to pyrimidine as an antimicrobial agent in medicinal chemistry.

2. Methods

2-1. Data source and Data collection

The primary data repository employed for this study was the Scopus database. To mitigate any potential biases arising from database updates, the literature search was meticulously conducted on the same day. The search methodology employed is detailed in Figure 1. Exclusive inclusion criteria encompassed original articles and reviews, with no constraints imposed on the timeframe under consideration. This approach aims to ensure a comprehensive examination of relevant literature without temporal limitations. Subsequently, pertinent details from each article, comprising the author's name, article source, abstract, year of publication, article title, and affiliation, were carefully extracted and organized in.csv format for further analysis.

2-3. Data Extraction

The exported data files were imported into Microsoft Excel 365 (Microsoft, USA), where two researchers independently conducted the screening process to determine the inclusion or exclusion of articles. Initially, the selection was initiated based on the article titles. Subsequently, the chosen articles underwent a thorough assessment, involving the reading of their abstracts and, subsequently, a comprehensive examination of the full text. The data extracted from the selected papers encompassed key information such as authors' names, article titles, article sources, affiliations, publication years, keywords, and the number of citations. In cases of any discrepancies between the researchers, discussions were undertaken to reconcile and reach a consensus.

2-4. Data analysis and visualization

The data underwent manual analysis utilizing Microsoft Excel 365 (Microsoft, USA) to statistically determine publication trends per year, prolific authors, countries and institutions, influential journals, and prevalent keywords. Visualization and representation of data relationships were done using VOSviewer (http://vosviewer.com), a software tool designed for visualizing networks within the scientific literature. This powerful tool facilitates the interconnection of journals, authors, and countries, providing insights into co-authorship, citations, co-citations, and co-occurrence analyses.

3. Results

3-1. Global Trend and Citation

A comprehensive retrieval from Scopus yielded a total of 1023 articles. However, after meticulous screening based on inclusion criteria, 934 articles were deemed eligible, comprising 867 research papers and 67 reviews with a total of 11060 citations and with average of 14.46 citations per paper. Figure 2 illustrates the dynamic trajectory of global publications on pyrimidine as an antimicrobial agent from 2015 to 2023. Notably, the years 2019 and 2022 emerged as peak periods, with each boasting 125 publications, showcasing a discernible trend over the specified timeframe.

3-2. Contribution of Countries

The global distribution of published articles is visually represented in Figure 4, with contributions from a total of 53 nations on the discussed topic. Table 1 outlines the top 10 countries in terms of both article count and total citations. Notably, India led the pack with 309 publications, followed by Egypt (181), China (101), Saudi Arabia (95), and the United States (76).

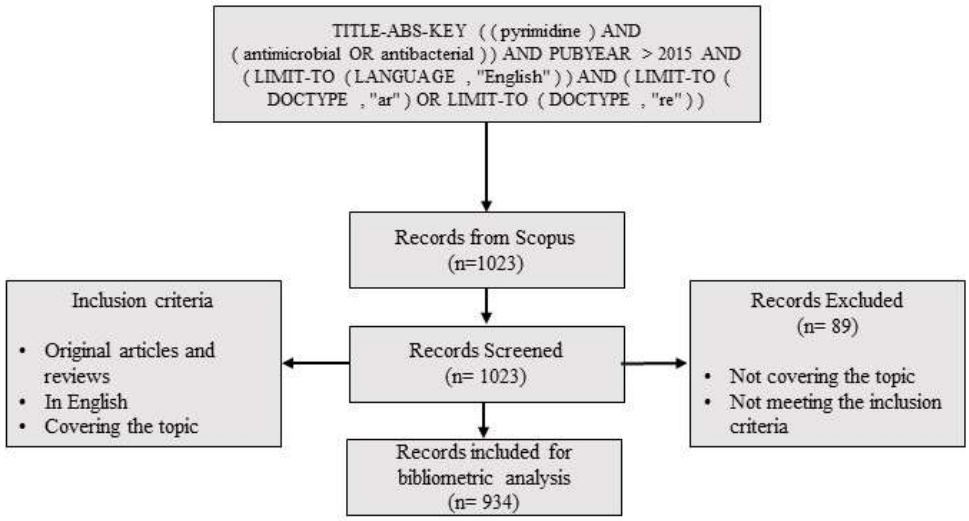

Figure 1. Overall search strategy for bibliometric analysis

In terms of international collaboration, India emerged as the most active collaborator, with Egypt and China closely following, as indicated by total link strengths (TLS) of 76, 94, and 20, respectively, in the co-authorship analysis (Figure 3). Interestingly, although China didn't have the highest publication count (101), it was noteworthy for having the most citations per publication (17.24), surpassing the United States (17.08) and the United Kingdom (16) in this regard.

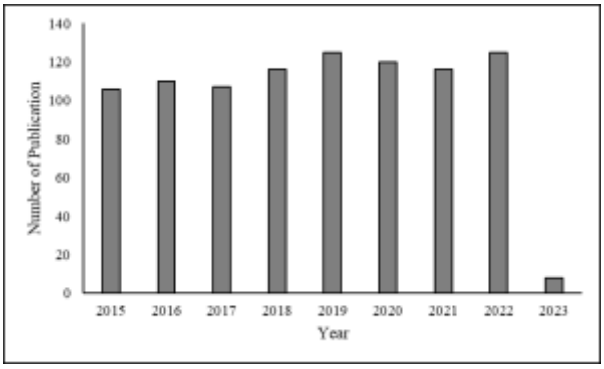

Figure 2. Number of publications per year on the topic (2015-2023).

An expansive collaborative effort involving 35 institutions worldwide has significantly contributed to the topical research, with each institution contributing a minimum of three publications. Table 3 provides a detailed overview of the leading organizations, showcasing those with five or more publications along with their respective overall citation counts. Notably, Cairo University and Zagazig University of Egypt stand out with an impressive combined total of 11 articles, making them the leading contributors. Following closely are Assiut University of Egypt (n = 8 and n = 6), Zabol University of Iran (n = 5), and Rutgers New Jersey Medical School of the United States (n = 5).

Cairo University of Egypt claims the highest total citations, accumulating 140 citations from its 11 publications. Meanwhile, Mansoura University of Egypt boasts the highest number of cited articles per publication (16.75), outshining Cairo University of Egypt with 12.73 cited articles per publication. Visual representation in Figure 5 unveils additional insights, highlighting that Rutgers New Jersey Medical School, Maharshi Dayanand University of India, and Qassim University in Saudi Arabia exhibit the highest Total Link Strength (TLS), as discerned from the co-authorship analysis of institutions.

Table 1. Top 10 countries contributed to the topic.

Rank	Country	TP	%	TC	C/P
1	India	309	33.08%	3190	10.32
2	Egypt	181	19.38%	2075	11.46
3	China	101	10.81%	1741	17.24
4	Saudi Arabia	95	10.17%	1347	14.18
5	United States	76	8.14%	1298	17.08
6	Iran	43	4.60%	429	9.98
7	Russia	42	4.50%	188	4.48
8	Iraq	36	3.85%	117	3.25
9	United Kingdom	24	2.57%	384	16
10	France	17	1.82%	232	13.65
10	Spain	17	1.82%	255	15

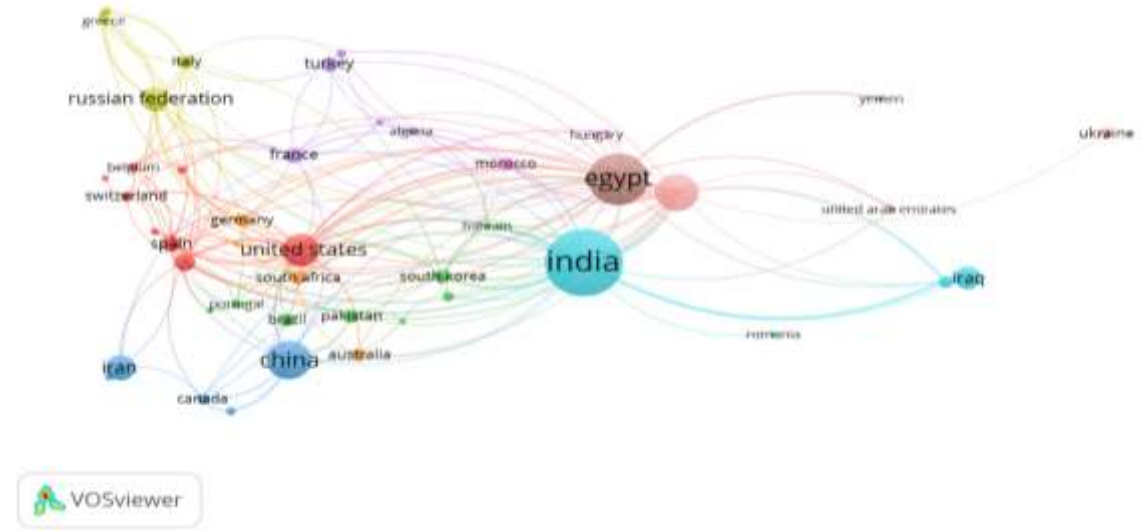

Figure 4. Countries co-authorship network

3-3. Contribution of institutions

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3-4. Contributions of Authors

The exploration of pyrimidine as an antimicrobial agent brought together a cadre of 35 authors hailing from diverse countries, each contributing a commendable minimum of five publications. Table 4 highlights the prominent authors driving the discourse, with a special focus on those who have made substantial contributions. Topping the list are Huang D. B. and Kumar S., each boasting an impressive 11 publications. Following closely are Shang R. (n = 10), Yi Y. (n = 9), and Ahmed M. (n = 8).

While Ahmed M. secures the lead with 8 publications, his work has garnered the most citations (113), surpassing El-Gazzar A.-R.B.A. and Hafez H., each accumulating 105 citations. The intricacies of collaboration among authors come to life in the visual representation of the co-authorship analysis (Figure 6), revealing four distinct groups of authors who collaborate extensively. At the network's core, Shang R., Yi Y., Fu Y., Liang G., and Liu Y. emerge as pivotal figures, each exhibiting Total Link Strengths (TLS) of 31, 27, 24, 20, and 17, respectively.

3-5. Journal Analysis

A total of 88 journals, each contributing a minimum of three articles, played a pivotal role in disseminating publications on the discussed topic. The cream of the crop is highlighted in Table 5, where the top 10 journals collectively published 278 articles. The Journal of Heterocyclic Chemistry takes the lead with an impressive 50 publications, followed closely by the European Journal of Medicinal Chemistry with 37 publications. Notably, the European Journal of Medicinal Chemistry emerges as the most cited, amassing a total of 1929 citations and a remarkable 52.14 citations per publication. Bioorganic and medicinal chemistry also stands out with 19 publications, 426 total citations, and 22.42 citations per publication. In the intricate network of sources visualized in Figure 7, the European Journal of Medicinal Chemistry dominates with 5 clusters, 23 links, and a Total Link Strength (TLS) of 51. Bioorganic Chemistry and Journal of Heterocyclic Chemistry follow suit with 4 clusters, 19 links, and TLS of 45, and 3 clusters, 17 links, and 32 TLS, respectively.

Table 3. Top contributed institutions

3-6. Keywords Analysis

Within the corpus of 934 articles, a rich tapestry of 783 total keywords emerged, each making a significant appearance in at least five journals. The top ten keywords, meticulously detailed in Table 6, encapsulate the thematic essence of the discourse. Notably, 'antibacterial activity' and 'nonhuman' stand out as the most recurrent, surfacing 534 and 468 times, respectively. Additionally, keywords such as 'Article,' 'Unclassified Drug,' 'Pyrimidine Derivative,' and 'Drug Synthesis' garnered frequencies of 461, 427, 381, and 369, respectively. The keyword 'antibacterial activity' takes center stage in Figure 8, exhibiting three clusters, 762 links, and an impressive Total Link Strength (TLS) of 15083, solidifying its status as the most frequently occurring keyword. Following closely is 'nonhuman,' boasting three clusters, 752 links, and a TLS of 15078.

Rank	Institution	TP	TC	C/P
1	Cairo University, Egypt	11	140	12.73
-	Zagazig University, Egypt	11	61	5.55
2	Assiut University, Egypt	8	84	10.5
3	University of Zabol, Iran	5	49	9.8
-	Rutgers New Jersey Medical School, US	5	18	3.6
4	Cairo University, Egypt	4	14	3.5
-	Islamic Azad University, Iran	4	45	11.25
-	Mansoura University, Egypt	4	67	16.75
-	Qassim University, Saudia Arab	4	31	7.75
-	Maharshi Dayanand University, India	4	31	7.75

TP=Total Publications; TC=Total Citation; C/P=Citation per Publication

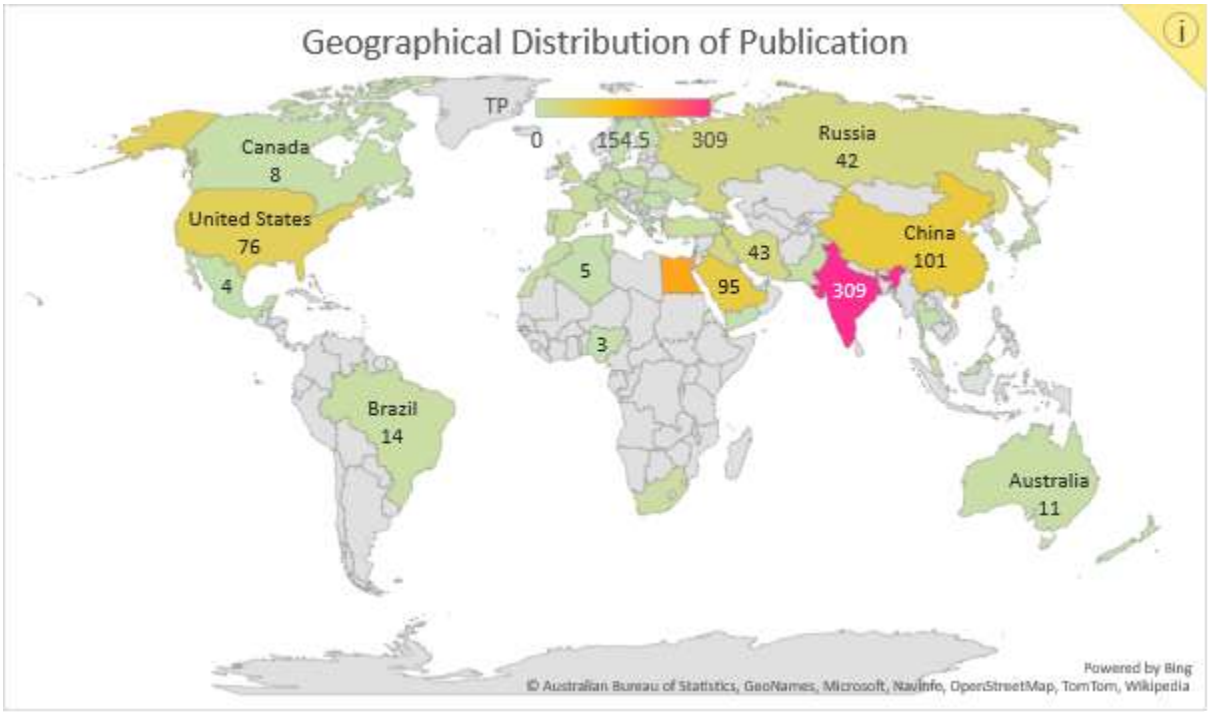

Figure 3. Global distribution of publications

Figure 5. Institutions co-authorship analysis

Table 4. Top authors contributed to the topic

Rank	Author Name	TP	TC	C/P
1	Huang D. B.	11	37	3.36
-	Kumar S.	11	103	9.27
2	Shang R.	10	67	6.7
3	Yi Y.	9	67	7.44
4	Ahmed M.	8	113	14.13
-	Beyzaei H.	8	71	8.88
-	Chen Y.	8	87	10.88
-	Desai N. C.	8	26	3.25
-	Fu Y.	8	67	8.38
-	Kumar A.	8	42	5.25
-	Liu Y.	8	102	12.75
5	El-Gazzar A.-R. B. A.	7	105	15
-	Fadda A. A.	7	45	6.43
-	Hafez H. N.	7	105	15
-	Li Y.	7	33	4.71

TP=Total Publications; TC=Total Citation; C/P=Citation per Publication

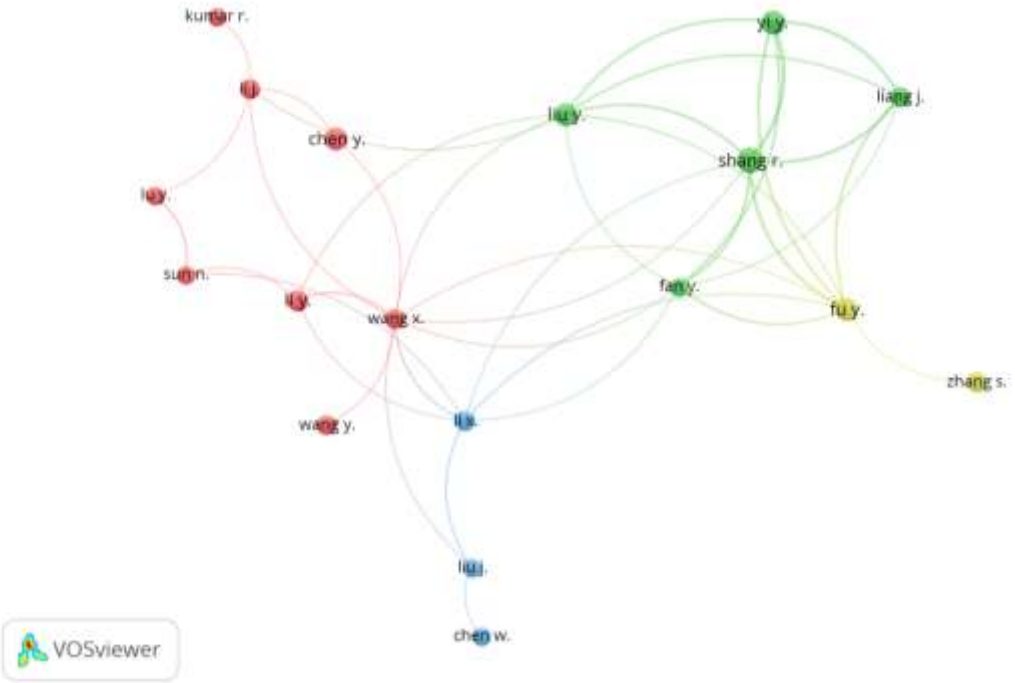

Figure 6. Authors co-authorship analysis

Table 5. Top 10 journals contributed to the topic

Rank	Source Title	TP	%	TC	C/P
1	Journal of Heterocyclic Chemistry	50	5.35%	363	7.26
2	European Journal of Medicinal Chemistry	37	3.96%	1929	52.14
3	Molecules	26	2.78%	330	12.69
4	Bioorganic Chemistry	25	2.68%	492	19.68
5	Journal of Molecular Structure	24	2.57%	251	10.46
6	Synthetic Communications	22	2.36%	301	13.68
7	Bioorganic and Medicinal Chemistry	19	2.03%	426	22.42
-	Medicinal Chemistry Research	19	2.03%	266	14
8	Bioorganic and Medicinal Chemistry Letters	15	1.61%	290	19.33
9	Chemistry Select	14	1.5%	134	9.57
-	Der Pharma Chemical	14	1.5%	35	2.5
10	Research Journal of Pharmacy and Technology	13	1.39%	31	2.38

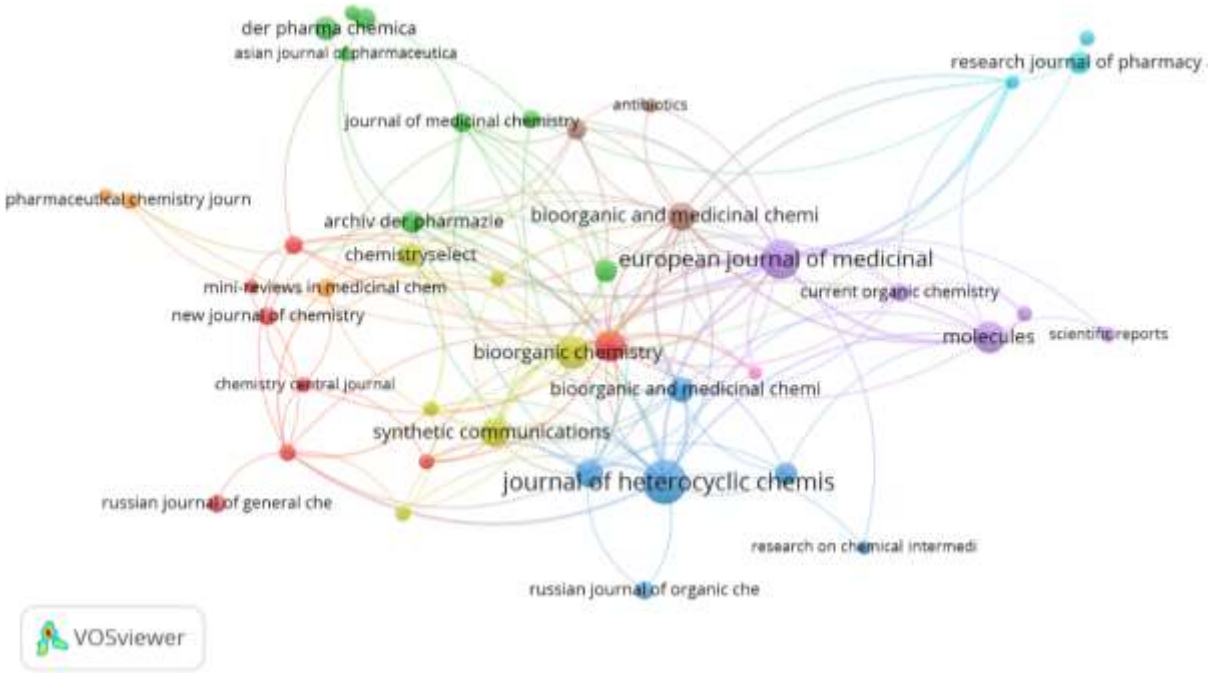

Figure 7. Journals network analysis

Table 6. Trending keywords on the topic

Rank	Keyword name	TP	%
1	Antibacterial activity	534	57.17%
2	Nonhuman	468	50.11%
3	Article	461	49.36%
4	Unclassified drug	427	45.72%
5	Pyrimidine derivative	381	40.79%
6	Drug synthesis	369	39.51%
7	Anti-infective agent	348	37.26%
8	Controlled study	341	36.51%
9	Escherichia coli	275	29.44%
10	Staphylococcus aureus	266	28.48%

TP= total publications

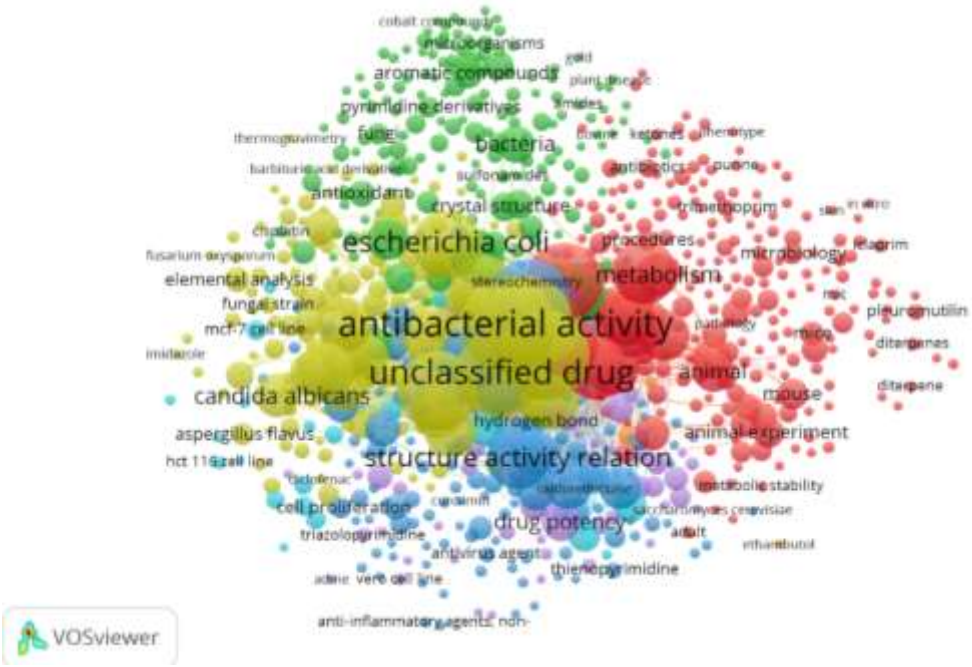

Figure 8. Keywords co-occurring analysis

4. DISCUSSION

Pyrimidines and their derivatives find diverse applications, with a significant focus on biological treatment processes (21, 22). Certain derivatives like plicacetin, Nikkomycin, and Bacimethrin exhibit antimicrobial and antifungal activities (23). Moreover, various pyrimidine derivatives serve as antibacterial drugs, such as sulfadiazine, sulfamerazine, and sulfadimidine, employed in treating conditions like acute urinary tract infections and cerebrospinal meningitis (24). The broad medicinal applications of pyrimidines can be attributed to the presence of pyrimidine bases in thymine, cytosine, and uracil, which are fundamental building blocks of nucleic acids, DNA, and RNA. Pyrimidines, notably active substances, demonstrate diverse biological actions, including in vitro activity against DNA and RNA, viruses, diuretics, anti-tumor, anti-HIV, and cardiovascular effects (5, 25).

This makes the pyrimidine base a focal point for medicinal chemists seeking to develop new antimicrobial drugs with a pyrimidine ring.

In this study, a bibliometric approach was employed to analyze publications from 2015 to March 2023 discussing pyrimidine as an antimicrobial agent. Examining 934 documents out of a total of 1023, trends over this period were studied based on various parameters. The most prominent nations, organizations, publications, and researchers were identified. The analysis identified the most prominent nations, organizations, publications, and researchers in the field. Using performance analysis and science mapping, the study identified topics regularly explored, topics needing further research, and upcoming popular topics. A significant number of 867 research articles on pyrimidine as an antimicrobial agent listed on the Scopus database underscores the global importance of the topic. The publication count showed a yearly increase, peaking in 2019 and 2022, with a noticeable decline in 2020 and 2021, likely due to the COVID-19 pandemic. However, the study's limitation lies in considering only articles published after 2015 and in English, which may omit significant contributions in other languages or earlier works.

The international scope of research was evident, with leading contributions from Asia, particularly India, China, Saudi Arabia, the Russian Federation, Iran, and Iraq. Network mapping revealed close collaborations among different countries, emphasizing the global importance of pyrimidine research.

Coauthorship analysis and Total Link Strength (TLS) were utilized to analyze collaborations between authors and institutions. This coauthorship analysis highlighted extensive research networks on pyrimidine as an antimicrobial agent, indicating collaborative efforts across institutions, countries, and authors. Cairo University in Egypt emerged as the most productive organization, followed closely by Zagazig University in Egypt. Moreover, the authors' analysis shows that researchers from different countries and institutions are working together on the antimicrobial activity of pyrimidine, which can extend the scope of the research and its importance. Journal analysis revealed that 88 journals published 278 articles on this topic, with the Journal of Heterocyclic Chemistry, European Journal of Medicinal Chemistry, and Molecules leading in publication volume and impact. These journals, with 2022 impact factors of 2.33, 6.7, and 4.9, respectively, demonstrate significant interest in publishing articles on pyrimidine, reflecting the widespread importance of this research area. Keyword cooccurrence analysis identified "antimicrobial activity" as the most recurring keyword, reflecting the current trend in pyrimidine antimicrobial research (26).

The collaboration and productivity demonstrated in this study underline the global importance of advancing research on pyrimidine as an antimicrobial agent. This can surely help researchers in future research and give them a direction to find trends and better results. Future research should aim to include a broader range of publications, incorporating articles in various languages and older works to provide a more comprehensive overview. Expanding the database search to include other reputable databases will also enhance the inclusiveness and accuracy of the analysis.

The future of pyrimidine research is promising, with potential advancements in understanding and utilizing their antimicrobial properties. Further exploration into the molecular mechanisms underlying their biological activities could lead to the development of more effective antimicrobial agents. Additionally, interdisciplinary collaborations will likely play a crucial role in advancing this field, fostering innovation, and broadening the scope of pyrimidine applications in medicine.

CONCLUSION

This study pioneers the use of bibliometric analysis to explore pyrimidine's potential as an antimicrobial agent, conducting an in-depth examination of trends in academic literature from 2015 to 2023. Out of 1023 topics cataloged in the Scopus database, 934 articles align closely with pyrimidine's antimicrobial properties, with noticeable publication peaks in 2019 and 2022. Globally, India, Egypt, and China significantly contribute to research on pyrimidine as an antimicrobial agent, with 309, 181, and 101 publications, respectively. Leading institutions like Cairo, Zagazig, and Assiut universities in Egypt have emerged as key contributors. Recognizing notable figures in the scientific community, including Huang D.B., Kumar S., and Shang R., with 11, 11, and 10 publications and total citations of 37, 103, and 67, respectively, underscores their impactful contributions to advancing the understanding of pyrimidine as an antimicrobial agent. Serving as a valuable resource, this study provides a comprehensive overview of the current state and trends in

pyrimidine antimicrobial research, guiding researchers in the identification and selection of future research areas for continued exploration.

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