Journal of Natural Science Review

Vol. 2, No. 3, 2024, 1-16
https://kujnsr.com
e-ISSN: 3006-7804

Bibliometric Analysis of Pyrimidine Compounds with Anti-cancer Activity: Research Trends from 2015 to 2023

Muhammad Aman Azad[1], Abdul Jalil Nesar[2] and Ahmad Tamim Ghafari[3]✉

[1,2] Kabul University, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Afghanistan
[3] Kabul University, Department of Pharmacology, Faculty of Pharmacy, Afghanistan
✉E-mail: tamim.ghafari@yahoo.com (corresponding author)

ABSTRACT

Cancer remains one of the most pervasive diseases in the world, globally, leading to millions of fatalities annually. Currently, numerous anti-cancer treatments are available to address the various types of cancer. Pyrimidine, a class of heterocyclic nitrogenous compounds, holds substantial promise in anti-cancer drug development due to its structural similarity to the nucleotide base pairs found in DNA and RNA. This work aimed to conduct a bibliometric analysis of studies on pyrimidine compounds with anti-cancer characteristics. Using the Scopus database, we examined literature published between 2015 and 2023, explicitly concentrating on pyrimidine derivatives as potential anti-cancer agents. Data analysis such as network analysis, co-occurrence, and visualization were conducted utilizing VOSviewer 1.6.13. Nine hundred twenty-two papers altogether, including reviews and original research, discussing the anti-cancer activity of pyrimidine compounds were identified within the specified timeframe up to January 10, 2023. Among these, 922 journal articles were selected for further analysis. Results show that Egypt led in research productivity with 267 articles (28.96%), followed by India with 234 articles (25.38%), and China with 163 articles (17.68%). Cairo University in Egypt ranked first in institutional productivity with 9 articles (0.98%), while the journal Bioorganic Chemistry was the most prolific, publishing 62 articles (6.72%) on pyrimidine compounds with anti-cancer activity. The notable increase in publications on the anti-cancer activity of pyrimidine compounds in recent years underscores the significant interest they have garnered from both pharmaceutical and academic researchers. The data presented in this study will serve as a foundational reference for future comparative studies in this area.

ARTICLE INFO

Article history:

Received: June 28, 2024
Revised: August 24, 2024
Accepted: September 14. 2024

Keywords:

Pyrimidine; Anti-cancer; Bibliometric Analysis; Pyrimidine Derivatives; Heterocyclic compounds

To cite this article: Azad, M. A., Nesar, A. J., & Ghafari, A. T. (2024). Bibliometric Analysis of Pyrimidine Compounds with Anti-cancer Activity: Research Trends from 2015 to 2023. *Journal of Natural Science Review, 2*(3), 1-16. DOI: https://doi.org/10.62810/jnsr.v2i3.61

To link to this article: https://kujnsr.com/JNSR/article/view/61

INTRODUCTION

Cancer remains a significant global health concern, with chemotherapy and radiotherapy facing challenges due to multidrug resistance, hindering their effectiveness (Miller et al., 2019). The WHO's 2022 report indicates that there were 20 million fresh cases of cancer, 9.7

million deaths from the disease, and 53.5 million survivors five years after diagnosis. Despite improvements, 1 in 5 persons will eventually have cancer; 1 in 9 men and 1 in 12 women will pass away from the illness. 1.8 million fatalities from cancer, or 18.7% of all cancer-related deaths, were caused by lung cancer. Cancer of the colon (900,000 deaths, 9.3%), carcinoma of the liver (760,000 deaths, 7.8%), cancer of the breast (670,000 deaths, 6.9%), and carcinoma of the stomach (660,000 deaths, 6.8%) were the subsequent most common cancer-related deaths. Due to the absence of efficient and focused anti-cancer treatments, these numbers are still rising. Over 35 million additional cancer cases are expected by 2050, up 77% from forecasts in 2022, underscoring the severity of the situation.

The search for novel cancer-fighting compounds relies heavily on heteroatoms, particularly heterocyclic building blocks. This highlights heterocycles' critical role in medication discovery, as nitrogen-containing heterocyclic compounds are commonly found in hormones, vitamins, and antibiotics (Heravi and Zadsirjan, 2020).

FDA records show that 60% of small-molecule medicines contain nitrogen-containing heterocycles, demonstrating the structural significance of these compounds in medicinal design and discovery (Ajani et al., 2017; Martins et al., 2015). Nitrogen heterocycles are commonly found in physiologically active chemicals due to their capacity to establish hydrogen bonds with DNA and their flexibility and stability in human tissue.

The anti-cancer properties of nitrogen-based heterocyclic compounds primarily stem from their ability to bind to genetic materials by forming hydrogen bonds (Özkay et al., 2010). Pyrimidine nuclei, with various substituents, are prevalent in FDA-approved medications and are known for their anti-cancer potential (Chiacchio et al., 2019). Pyrimidine derivatives, commonly present in the genome and Products from organic sources, are instrumental in cancer research, with the pyrimidine backbone structure implicated in cancer pathogenesis (see Figure 1).

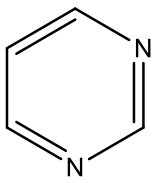

Figure 1. Fundamental ring structure of pyrimidine.

Early in the history of organic chemistry, pyrimidines gained notoriety as "m-Diazine" byproducts of the catabolism of uric acid. Brugnatelli developed alloxan, the first pyrimidine derivative, in 1818 by oxidizing nitric acid with uric acid (Lagoja et al., 2005).

Pyrimidine is a heterocycle member that includes nitrogen (Selvam et al., 2015). Pyrimidines have two nitrogen atoms at positions one and three in the heterocyclic six-membered aromatic ring, like benzene and pyridine. Pyridinium's melting and boiling temperatures, a monochromatic substance, are 22.5 °C and 124 °C, respectively. It is also

possible to generate pyrimidines by hydrolyzing nucleic acids, namely uracil, thymine, and cytosine. Pyrimidines constitute an important class of chemicals with a broad range of biological activities, including analgesics, COX inhibitors, and anti-cancer effects (Gondkar et al., 2013).

Pyrimidines are synthetically versatile and may be used to create a wide range of structurally varied derivatives, including analogs that are the result of substituting an aryl ring, nitrogen derivatization in the pyrimidine, and substitutions at carbon positions 2, 4, 5, and 6 (Selvam et al., 2015).

Based on pharmacological investigations, some natural herbal fruit like Ziziphus Jujuba has anti-cancer properties (Ayoubi et al., 2024). Pyrimidine derivatives have long been known to provide therapeutic effects in medicinal chemistry. Numerous pyrimidine analogs have evolved into commonly used chemotherapeutic agents. Different sources of substituted pyrimidines, including plants, animals, microorganisms, and marine organisms, are identified and produced for medicinal purposes. Pyrimidine derivatives target proteins such as the EGFR tyrosine kinase, Janus kinase, Mitotic Checkpoint Protein Kinase (Mps1), carbonic anhydrase, and MDM-2. They can cause caspase 3 activation and lower Mcl-1 protein levels, which inhibit apoptosis and cause cancer cells to die. They also exhibit notable selectivity for CDK9 relative to other CDKs (Shao et al., 2013).

Due to its success in treating several grave illnesses, such as myelo leukemia, pulmonary fibrosis caused by idiopathic factors, and carcinoma of the breast, pyrimidine derivatives have attracted a lot of interest in modern medical research (Prachayasittikul et al., 2017; Chiacchio et al., 2019). Examples of commercially available medications containing pyrimidine moieties include Gemcitabine (Figure 2A), 5-Fluorouracil (Figure 2B), and Floxuridine (Figure 2C).

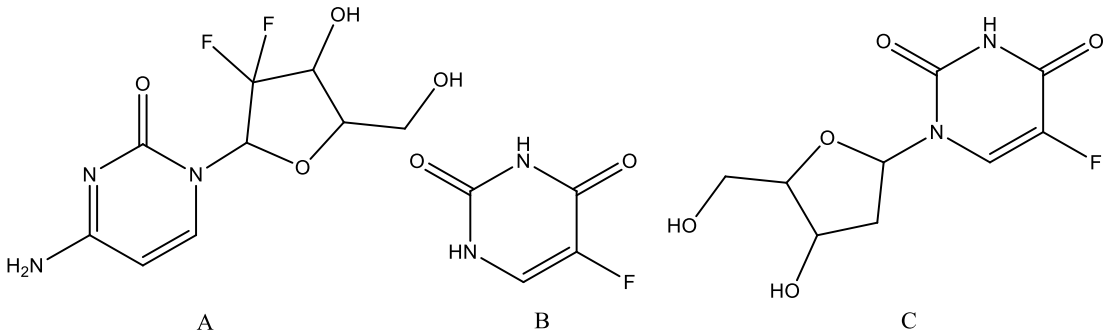

Figure 2. Anti-cancer drugs containing pyrimidine moieties (A-C) are available on the market.

The utilization of pyrimidine derivatives in pharmaceuticals and agricultural chemicals is deemed essential. Pyrimidines play a crucial role in effectively treating various disorders. Aside from their application in thyroid and leukemia medications, pyrimidine derivatives demonstrate a myriad of remarkable biological properties, including anti-cancer, antimicrobial, and antifungal activities (Patel et al., 2012).

When the volume of research on a particular topic, such as cancer, is vast, it can be challenging for researchers to structure a comprehensible review with pertinent information. Bibliometrics serves as a tool for staying current through thorough searches and technological advancements, offering a broad overview and qualitative and quantitative analysis of scientific publications (Zhu et al., 2020). This involves tracking the rate of scientific advancement in a specific topic over time, summarizing interactions among participants, and enabling investigation into the contributions of productive nations, organizations, journals, and subject areas (Zhu et al., 2021).

Bibliometric analysis employs mathematical and statistical techniques to qualitatively and quantitatively assess the progression of research activities within a specific field. This method can track and predict development trends over a defined period. Furthermore, it evaluates the contributions of authors, institutions, and countries, helping to identify research trends, gaps, and upcoming paths in the area.

This paper aims to provide a bibliometric examination of the body of knowledge about pyrimidine compounds' anti-cancer properties. By examining the trends and significance of these compounds in pharmaceutical science, the study seeks to highlight their potential and identify key areas for future research.

METHODS AND MATERIALS

Data Source and Data Collection

The Scopus database served as the primary tool for gathering the most pertinent documents concerning pyrimidine anti-cancer research. Data retrieval occurred on January 10, 2023. The search methodology, delineated in Figure 3, was employed, refining the search to articles and reviews exclusively. Details, including author names, article titles, publication sources, affiliations, publication years, keywords, and abstracts for each article were exported in CSV format.

Data Extraction

The data files generated were imported into Microsoft Excel 365 (Microsoft, USA) for more analysis. Two independent researchers conducted the screening of publications for inclusion and exclusion. Initially, selections were made based on article titles. Subsequently, the abstracts and full texts of the chosen articles were reviewed for assessment. Information such as author names, article titles, affiliations, publication sources, publication years, keywords, and citation counts were extracted from the specific papers. Any disparities between the researchers' findings were resolved through discussion to reach a consensus.

Data Analysis and Visualization

The data underwent manual analysis using Microsoft Excel 365 (Microsoft, USA). Statistical analysis examined the number of publications per year, the most prolific authors, countries, institutions, journals, and keywords. VOSviewer version 1.6.19 (http://vosviewer.com), a software tool for visualizing scientific literature networks, was employed for visualization and

network analysis. This tool facilitates co-authorship, citation, co-citation, and co-occurrence analyses, linking journals, authors, countries, and keywords (Wu et al., 2021).

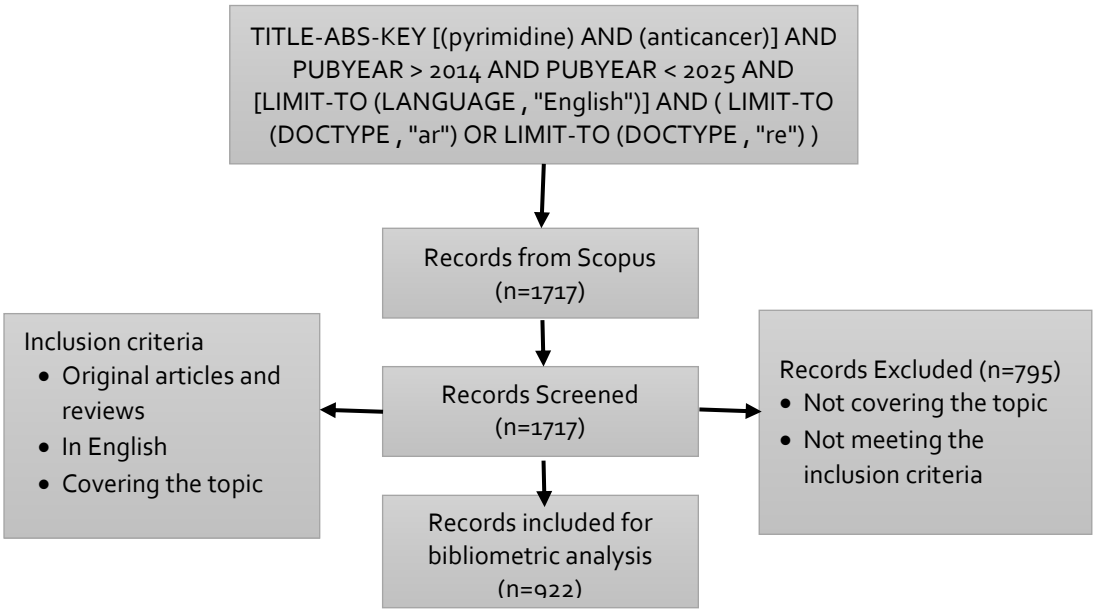

Figure 3. Overall search strategy for bibliometric analysis

FINDINGS

Global Trend and Citation

A total of 922 documents related to pyrimidine with anti-cancer properties were cataloged in the Scopus database between 2015 and January 10, 2023. Figure 4 illustrates the progression of publication numbers over this period. A clear upward trend in research outputs is evident from 2015 to January 10, 2023, indicating a steady increase in scholarly activity in this field. The papers were cited in a total of 1408 on average, 1.52 per paper.

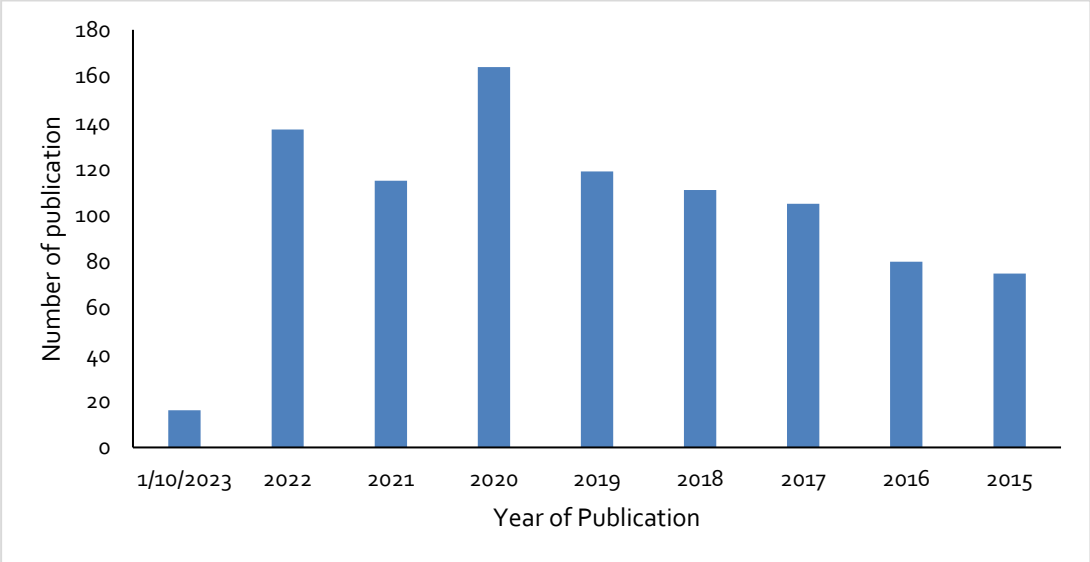

Figure 4. Number of publications per year

Contribution of Countries

Figure 5 depicts the global distribution of published articles related to pyrimidine anti-cancer research, showcasing contributions from a total of 72 countries. Table 1 presents the top 10 countries with the highest number of publications, along with their respective total citation counts. Egypt emerged as the leading contributor with 267 publications, followed by India with 234, China with 163, Saudi Arabia with 134, and the United States with 70 publications. Regarding collaborative efforts (as shown in Figure 6), Egypt exhibited the strongest collaboration with other countries, followed by India, with total link strengths (TLS) of 151 and 64.

Table 1. Top 10 countries contributed to the topic

Rank	Country	TP	%	TC	C/P
1	Egypt	267	28.96%	3515	13.16
2	India	234	25.38%	3119	13.33
3	China	163	17.68%	1746	10.71
4	Saudi Arabia	134	14.53%	1460	10.90
5	United States	70	7.59%	1049	14.99
6	South Korea	36	3.90%	563	15.64
7	Poland	28	3.04%	237	8.46
8	Turkey	25	2.71%	216	8.64
9	Iran	24	2.60%	187	7.79
9	Italy	24	2.60%	305	12.71
10	Germany	17	1.84%	189	11.12

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

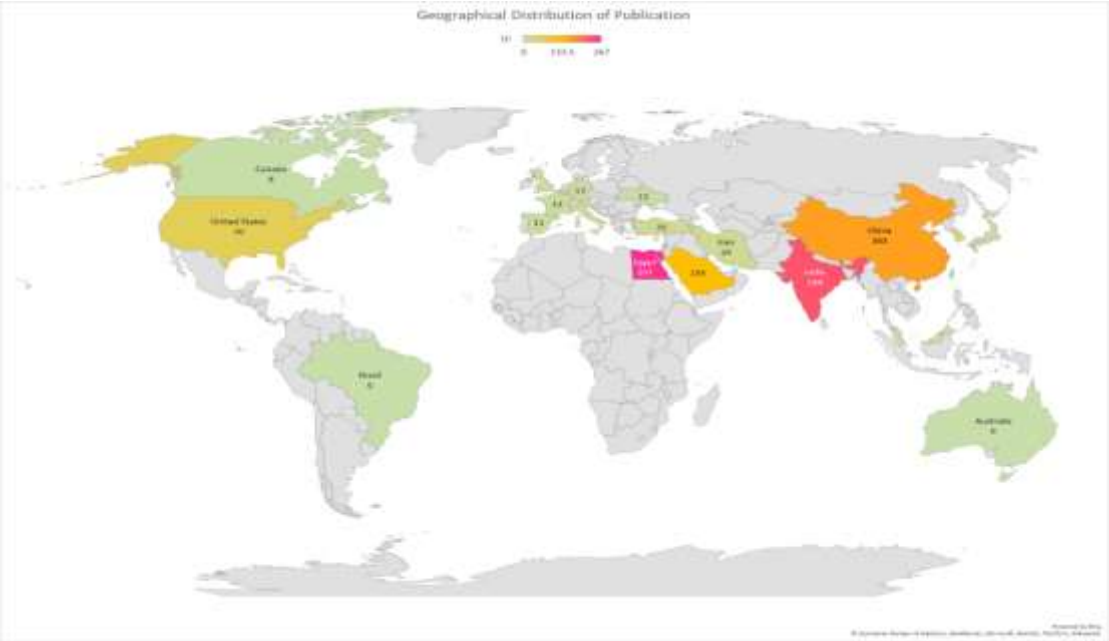

Figure 5. Global distribution of publications

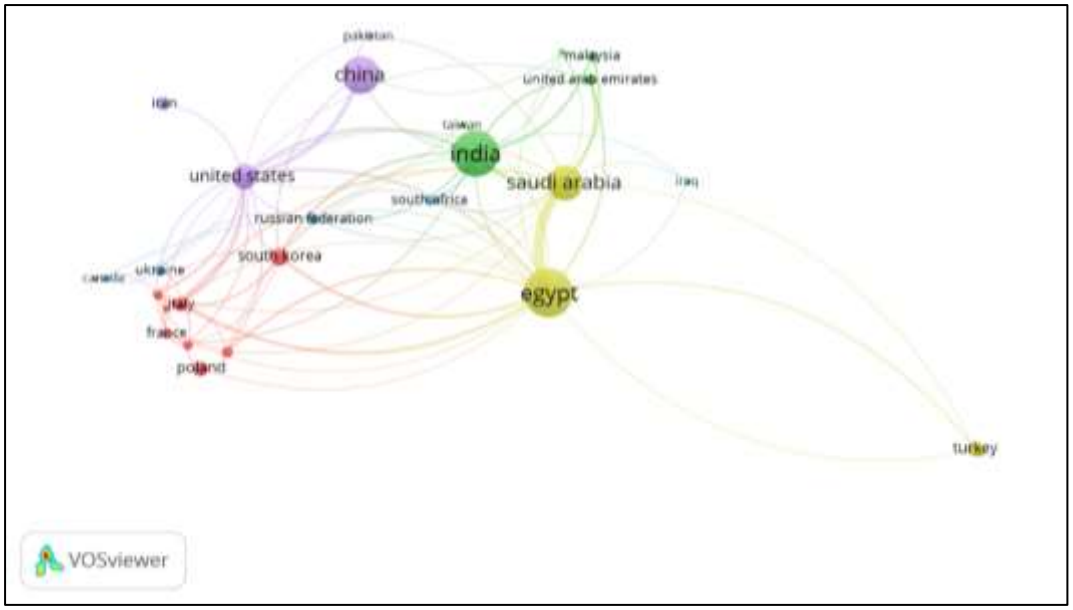

Figure 6. Countries co-authorship network

Contribution of Institutions

A total of 2595 institutions have contributed to research on the topic. Table 2 enumerates the top institutions with five or more publications and their respective citation counts. Leading the list is the Department of Chemistry, Faculty of Science, Cairo University in Egypt, with 9 publications, followed by the Department of Medicinal Chemistry, Faculty of Pharmacy, Mansoura University (8 publications), also in Egypt, and the Faculty of Chemistry, Nicolaus Copernicus University (7 publications) in Poland. Notably, the Faculty of Pharmaceutical Sciences, Maharshi Dayanand University in India, with 7 publications, garnered the highest total citations (186).

Furthermore, in the institutional analysis, the visualization (Figure 7) reveals 2 clusters encompassing 10 items and 39 links. The cluster highlighted in red exhibits the most items (8 items). Additionally, the Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Beni-Suef University, Beni-Suef in Egypt, displayed the highest total link strength (TLS) of 5.

Table 2. Top contributed institutions

Rank	Institution	TP	TC	C/P
1	Department of Chemistry, Faculty of Science, Cairo University, Giza, 12613, Egypt	9	78	8.6667
2	Department of Medicinal Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura, 35516, Egypt	8	151	18.875
3	Faculty of Chemistry, Nicolaus Copernicus University, Gagarina 7, 87-100, Poland	7	70	10
3	Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Beni-Suef University, Beni-Suef, 62514, Egypt	7	128	18.2857

3	Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura, 35516, Egypt	7	142	20.2857
3	Faculty of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, 124001, India	7	186	26.5714
3	Guangdong Provincial Key Laboratory of New Drug Screening, School of Pharmaceutical Science, Southern Medical University, Guangzhou, 510515, China	7	149	21.2857
4	Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt	6	94	15.6667
4	School of Pharmaceutical Sciences, Zhengzhou University, Zhengzhou, 450001, China	6	34	5.6667
5	Chemistry Research Centre, Mohamed Sathak Engineering College, Kilakarai, Ramanathapuram, Tamil Nadu 623 806, India	5	156	31.2

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

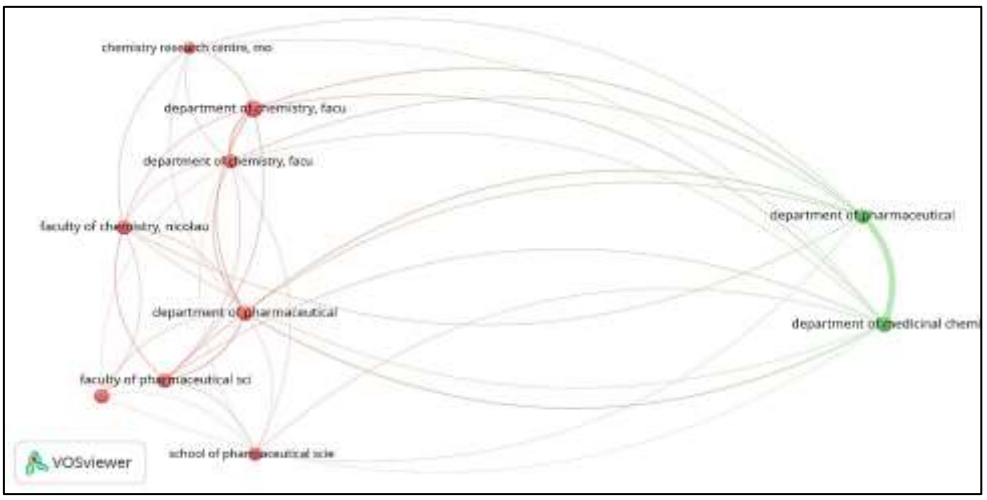

Figure 7. Institutions co-authorship analysis

Contributions of Authors

A total of 4097 authors from various countries contributed to publications on pyrimidine anti-cancer activity. Table 3 highlights the top authors who made significant contributions. Liu Y. and Zhang J. are leading the list, each with 15 publications and respective total citation counts of 292 and 114. Sankarganesh M. ranked second with 14 publications, amassing the highest citations (297), followed by Abouzid K.A.M., Awad H.M., El-Sayed W.A., and Kumar S., each with 12 or 11 publications.

Regarding the author's analysis, the visualization network (Figure 8) reveals 6 clusters comprising 37 items and 155 links. Liu Y. and Zhang J. occupy central positions in the network, with respective total link strengths (TLS) of 25 and 24, indicating significant collaboration between them.

Table 3. Top authors contributed to the topic

Rank	Author Name	TP	TC	C/P
1	Liu Y.	15	292	19.47
1	Zhang J.	15	114	7.60
2	Sankarganesh M.	14	297	21.21
3	Abouzid K.A.M.	12	197	16.42
3	Awad H.M.	12	274	22.83
3	El-Sayed W.A.	12	175	14.58
4	Kumar S.	11	234	21.27
4	Li Y.	11	117	10.64
4	Wang J.	11	64	5.82
4	Zhang Y.	11	56	5.09
5	Schenone S.	10	90	9.00
5	Wang Y.	10	91	9.10
6	Akomska I.	9	135	15.00
6	Chen Y.	9	92	10.22
6	Dhaveethu Raja J.	9	174	19.33
6	Liu H.	9	45	5.00
6	Liu J.	9	102	11.33

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

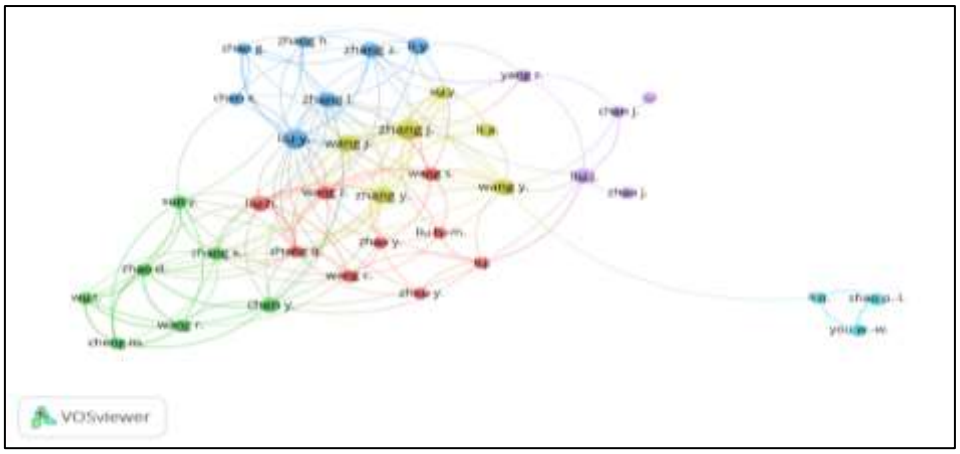

Figure 8. Authors co-authorship analysis

Journal Analysis

A total of 261 journals have published extracted publications on the topic. The top 10 journals have collectively published 324 articles (as shown in Table 4). The Journal of Bioorganic Chemistry leads the list, with 62 publications and a remarkable total citation count of 1235. The European Journal of Medicinal Chemistry secured the second position with 58 publications, followed by Molecules (35 publications), Journal of Heterocyclic Chemistry (33 publications), and Bioorganic and Medicinal Chemistry Letters (31 publications).

Regarding the journal analysis, the visualization network (Figure 9) reveals 8 clusters comprising 42 items and 447 links.

Table 4. Top journals contributed to the topic

Rank	Source Title	TP	%	TC	C/P
1	Bioorganic Chemistry	62	6.72%	1235	19.92
2	European Journal of Medicinal Chemistry	58	6.29%	1653	28.50
3	Molecules	35	3.80%	299	8.54
4	Journal of Heterocyclic Chemistry	33	3.58%	285	8.64
5	Bioorganic and Medicinal Chemistry Letters	31	3.36%	544	17.55
6	Journal of Molecular Structure	30	3.25%	225	7.50
7	Anti-Cancer Agents in Medicinal Chemistry	22	2.39%	223	10.14
8	Medicinal Chemistry Research	20	2.17%	213	10.65
9	Bioorganic and Medicinal Chemistry	17	1.84%	297	17.47
10	Synthetic Communications	16	1.74%	294	18.38

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

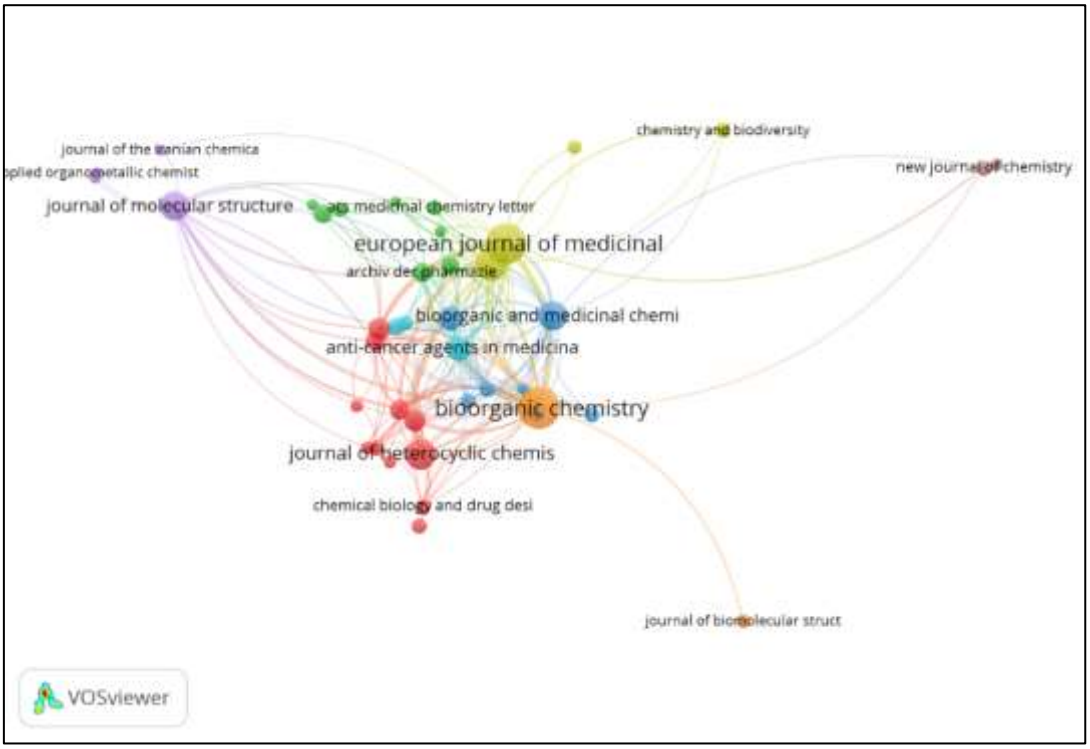

Figure 9. Journals co-authorship analysis

Keywords Analysis

A total of 885 keywords were identified across 922 papers, occurring a total of 24,902 times. The top ten keywords are outlined in Table 5. Among them, "human," "antineoplastic agent," and "pyrimidine derivative" were the most frequently occurring keywords, with 594, 499, and 474 instances, respectively. Other commonly used keywords included "unclassified drug," "antineoplastic activity," "drug synthesis," "human cell," "chemistry," "antineoplastic agents," and "pyrimidines," with occurrences of 459, 407, 403, 395, 372, 363, and 353, respectively.

Regarding keyword analysis, the visualization network (as depicted in Figure 10) reveals 8 clusters comprising 885 items and 107,852 links.

Table 5. Top most occurred keywords

Keywords	TO	%
human	594	64.43%
antineoplastic agent	499	54.12%
pyrimidine derivative	474	51.41%
unclassified drug	459	49.78%
antineoplastic activity	407	44.14%
drug synthesis	403	43.71%
human cell	395	42.84%
chemistry	372	40.35%
antineoplastic agents	363	39.37%
pyrimidines	353	38.29%

Note. TO=Total Occurrences

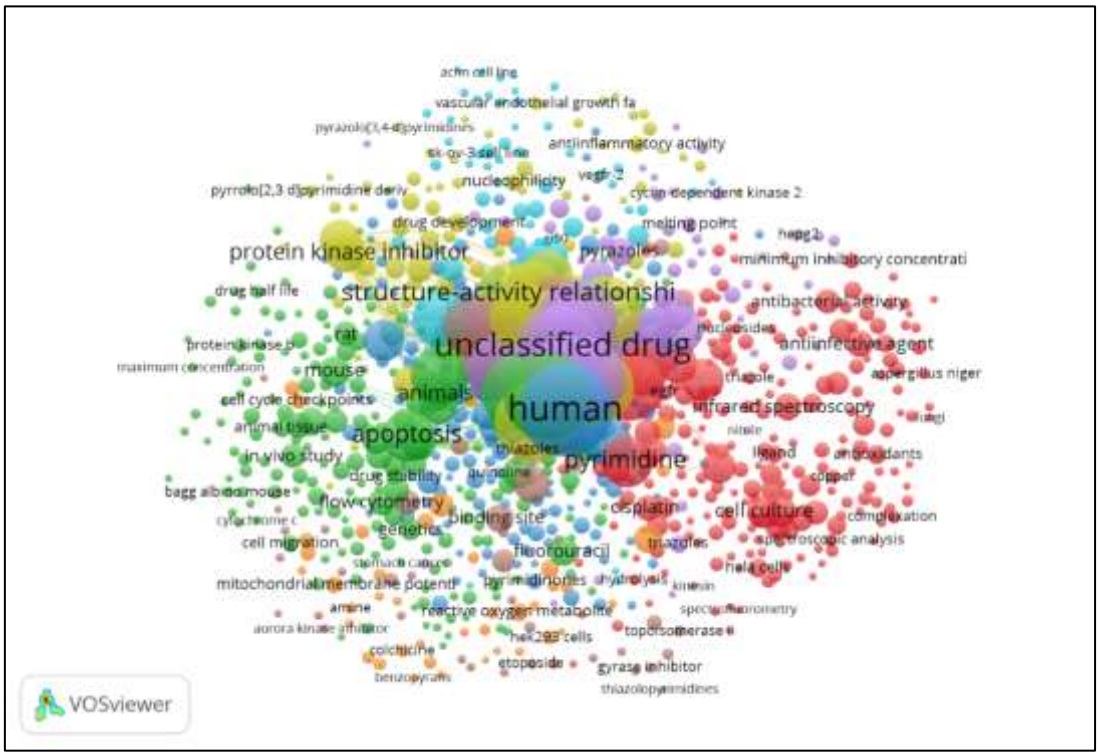

Figure 10. Keywords co-authorship analysis

DISCUSSION

The compounds produced from the pyrimidine scaffold display numerous pharmacological activities, such as anti-inflammatory, antibacterial, antiviral, antidiabetic, and anti-cancer effects. Notable drugs based on pyrimidine analogs encompass antibacterial agents like sulfadiazine and trimethoprim, antivirals such as trifluridine and idoxuridine, anti-HIV treatments such as stavudine and retrovir (zidovudine), anti-tuberculosis pharmaceuticals such as viomycin, anti-malarial such as sulfadoxine, and anti-cancer therapies such as 5-fluorouracil (Tylińska et al., 2021).

In this study, we aimed to conduct a bibliometric analysis of recent research on pyrimidine anti-cancer agents from 2015 to January 10, 2023. Utilizing the widely recognized Scopus database, previously employed in bibliometric studies (Sweileh et al., 2016). The study analyzed 922 documents from 1717, examining trends across various parameters. Notable nations, organizations, publications, and researchers in this domain were identified, shedding light on the significant contributors to the field. Key authors, institutions, countries, and publications on pyrimidine anti-cancer research were acknowledged. Through performance analysis and science mapping, we identified recurring themes explored by authors, areas requiring further investigation, and emerging topics of interest. The substantial presence of 842 research articles on pyrimidine anti-cancer agents in the Scopus database underscores the global significance of this field, with publication counts showing an increasing trend over the years. Co-authorship analysis and Total Link Strength (TLS) were employed to assess collaborations between authors, institutions, and countries. Notably, Cairo University in Egypt emerged as the most prolific and influential organization in this realm, closely followed by Mansoura University in Egypt, which published 128 articles emphasizing the widespread interest in this topic. Consequently, Egypt holds a significant position in this field.

Research on Structure-Activity Relationships (SAR) provides information on the molecular characteristics determining receptor selectivity and affinity. Understanding a compound's potential by changing its hydrophobic domain is frequently possible. Usually consisting of an aryl ring, this domain becomes more active upon adding electron-donating and electron-withdrawing groups at ortho, meta, and para locations. Substituted compounds generally exhibit greater potency than their unsubstituted counterparts, likely due to their improved fit within the receptor site. Key investigations, including those by (Estrada and Pena, 2000; Bruno-Blanch et al. 2003), consistently highlight crucial core fragments characterized by hydrogen donor/acceptor units, hydrophobic domains (A) (substituted or unsubstituted aryl rings), and electron donor atoms (D). The structures of well-known pyrimidine medications exhibited the following characteristics (see Fig 4).

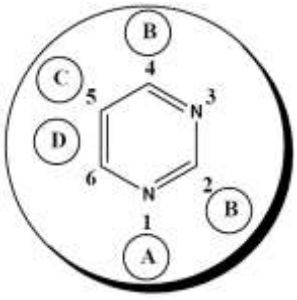

Figure 11. SAR of pyrimidine-marketed drugs

A: Substituting members within a saturated heterocyclic ring with five positions yields compounds with antiviral and anti-cancer effects.

B: Replacement of a six- or five-membered saturated heterocyclic ring at the second position results in anthelmintic properties, expectorant effects for anti-parkinsonism, and therapeutic benefits for peripheral neuropathies and gastrointestinal disturbances.

B: Introduction of amino groups at the second and fourth positions of the keto group, referred to as mixed keto or keto group substitution, yields compounds with anti-cancer, antiviral, antibacterial, and antifungal properties, along with treatments for liver disorders and respiratory tract infections.

C: Substituting a saturated distal heterocyclic ring, substituted amine, or halogen at the fifth position leads to compounds with antibacterial and anti-cancer properties.

D: Combining substitution at ortho, meta, and para locations in the distal aryl ring with fusion of heterocyclic rings at the fifth and sixth positions yields compounds that have antiviral, antibacterial, anti-cancer, vasodilator, and urinary tract infection therapeutic capabilities.

Inhibition of nucleoside phosphorylases and nucleosidases, Hsp90 inhibition, cyclin-dependent kinase inhibition, Akt inhibition, FAK/Pyk2 inhibition, MPS1 kinase inhibition, PI3K inhibition, tropomyosin-related kinase inhibition, EGFR modulation, mTOR selective kinase inhibition, and histone deacetylase inhibition are just a few of the diverse mechanisms through which patented pyrimidines have demonstrated their anti-cancer potential. The mechanism that has been studied the most among them is kinase inhibition. With remarkably low IC50 values, several pyrimidines, including pyrazolo pyrimidines, pyrrolo [2,3-d] pyrimidine, 5,7-substituted-imidazo[1,2-c] pyrimidine, cyano-substituted thieno [2,3-d] pyrimidines, and thieno [3,2-d], have demonstrated amazing cell-killing capacity in a variety of scaffolds. Pyrimidine, pyridopyrimidine derivatives, pyrimidine-based biaryl compounds, disubstituted 5-fluoro pyrimidine derivatives, and pyrido [2,3-d] pyrimidine-7-ones (Kaur et al., 2015). Furthermore, research suggests that adding a (hydroxyalkyl) or [(dialkylamino)alkyl] amino side chain to these medications increases their anti-cancer efficacy (Tylińska et al., 2021). These classes are attractive as future therapeutic candidates because of their anti-cancer effects at nanomolar doses, highlighting the need for more preclinical and clinical research. This compilation might benefit medicinal chemists investigating pyrimidine derivatives' anti-cancer potential.

CONCLUSION

This study compiled a total of 1717 papers published from January 2015 to January 10, 2023, aiming to showcase the progress in research. Among these, 922 articles closely focused on pyrimidine anti-cancer properties. The fact that more papers about pyrimidine anti-cancer activity have been published in recent years demonstrates how much interest the pyrimidine scaffold has attracted from academic and pharmaceutical experts. According to the data, Professor Liu Y. has the most significant publications and is the most essential author on the subject. Regarding academic institutions, Cairo University's Department of Chemistry, Faculty of Science, has emerged as a paper number and quality leader. Active countries in

this research domain included Egypt, India, and China. This bibliometric analysis elucidated various mechanisms of pyrimidine's anti-cancer activity explored in publications. The data presented in this study will serve as foundational information for future comparative studies.

Conflict of Interests: The authors declare no conflict of interests.

REFERENCES

Ajani, O. O., Audu, O. Y., Aderohunmu, D. V., Owolabi, F. E., & Olomieja, O. A. (2017). Undeniable pharmacological potentials of quinazoline motifs in therapeutic medicine. *American Journal of Drug Discovery and Development, 7,* 1-24. http://dx.doi.org/10.3329/bjp.v11i3.25731

Ayoubi, R., Foladi, M. M., Lutfi, S., & Zhakfar, A. M. (2024). Determination of Phenolic and Flavonoid Content in Ziziphus Jujuba Mill. Fruit Collected from Farah Province, Afghanistan. *Journal of Natural Science Review, 2*(1), 21-33. http://doi.org/10.62810/jnsr.v2i1.27

Bruno-Blanch L, Galvez J, Garcia-Domenac R (2003) Topological virtual screening: A way to find new anticonvulsant drugs from chemical diversity. *Bioorg Med Chem Lett 13* 2749-2754. https://doi.org/10.1016/s0960-894x(03)00535-3

Chiacchio, M. A., Iannazzo, D., Romeo, R., Giofrè, S. V., & Legnani, L. (2019). Pyridine and pyrimidine derivatives as privileged scaffolds in biologically active agents. *Current Medicinal Chemistry, 26*(40), 7166-7195. https://doi.org/10.2174/0929867325666180827154153

Estrada E, Pena, A (2000) In silico studies for the rational discovery of anticonvulsant compounds. *Bioorg Med Chem 8* 2755-2770. https://doi.org/10.1016/S0968-0896(00)00204-2

Gondkar, A. S., Deshmukh, V. K., & Chaudhari, S. R. (2013). Synthesis, characterization, and in-vitro anti-inflammatory activity of some substituted 1,2,3,4 tetrahydropyrimidine derivatives. *Drug Invention Today, 5*(3), 175-181. https://doi.org/10.1016/j.dit.2013.04.004

Heravi, M. M., & Zadsirjan, V. (2020). Prescribed drugs containing nitrogen heterocycles: An overview. *RSC Advances, 10*(72), 44247-44311. https://doi.org/10.1039/D0RA07203A

Kaur, R., Kaur, P., Sharma, S., Singh, G., Mehndiratta, S., MS Bedi, P., & Nepali, K. (2015). Anti-cancer pyrimidines in diverse scaffolds: A review of patent literature. *Recent Patents on Anti-Cancer Drug Discovery, 10*(1), 23-71. https://doi.org/10.2174/1574892810666150423103037

Lagoja, I. M. (2005). Pyrimidine as constituent of natural biologically active compounds. *Chemistry & Biodiversity, 2*(1), 1-50. https://doi.org/10.1002/cbdv.200590001

Miller, K. D., Nogueira, L., Mariotto, A. B., Rowland, J. H., Yabroff, K. R., Alfano, C. M., ... & Siegel, R. L. (2019). Cancer treatment and survivorship statistics, 2019. CA: *A Cancer Journal for Clinicians, 69*(5), 363-385. https://doi.org/10.3322/caac.21565

Martins, P., Jesus, J., Santos, S., Raposo, L. R., Roma-Rodrigues, C., Baptista, P. V., & Fernandes, A. R. (2015). Heterocyclic anti-cancer compounds: Recent advances and the paradigm shift towards the use of nanomedicine's toolbox. *Molecules, 20*(9), 16852-16891. https://doi.org/10.3390/molecules200916852

Özkay, Y., Işıkdağ, İ., İncesu, Z., & Akalın, G. (2010). Synthesis of 2-substituted-N-[4-(1-methyl-4,5-diphenyl-1H-imidazole-2-yl)phenyl]acetamide derivatives and evaluation of their anti-cancer activity. *European Journal of Medicinal Chemistry, 45*(8), 3320-3328. https://doi.org/10.1016/j.ejmech.2010.04.048

Patel, K. S., Raval, K. N., Patel, S. P., Patel, A. G., & Patel, S. V. (2012). A review on synthesis and biological activities of pyrimidine derivatives. *International Journal of Pharmacy and Biological Sciences, 2*(3), 170-182. http://dx.doi.org/10.1002/chin.201307207

Prachayasittikul, S., Pingaew, R., Worachartcheewan, A., Sinthupoom, N., Prachayasittikul, V., Ruchirawat, S., & Prachayasittikul, V. (2017). Roles of pyridine and pyrimidine derivatives as privileged scaffolds in anti-cancer agents. *Mini-Reviews in Medicinal Chemistry, 17*(10), 869-901. https://doi.org/10.2174/1389557516666161102144548

Selvam, T. P., James, C. R., Dniandev, P. V., & Valzita, S. K. (2015). A mini-review of pyrimidine and fused pyrimidine marketed drugs. *Research in Pharmacy, 2*(4), 1-9. https://api.semanticscholar.org/CorpusID:97744513

Shao, H., Shi, S., Foley, D. W., Lam, F., Abbas, A. Y., Liu, X., ... & Wang, S. (2013). Synthesis, structure-activity relationship, and biological evaluation of 2,4,5-trisubstituted pyrimidine CDK inhibitors as potential anti-tumor agents. *European Journal of Medicinal Chemistry, 70*, 447-455. https://doi.org/10.1016/j.ejmech.2013.10.014

Sweileh, W. M., Shraim, N. Y., Al-Jabi, S. W., Sawalha, A. F., Rahhal, B., Khayyat, R. A., & Sa'ed, H. Z. (2016). Assessing worldwide research activity on probiotics in pediatrics using Scopus database: 1994–2014. *World Allergy Organization Journal, 9*, 25. https://doi.org/10.1186/s40413-016-0120-8

Tylińska, B., Wiatrak, B., Czyżnikowska, Ż., Cieśla-Niechwiadowicz, A., Gębarowska, E., & Janicka-Kłos, A. (2021). Novel pyrimidine derivatives as potential anti-cancer agents: Synthesis, biological evaluation, and molecular docking study. *International Journal of Molecular Sciences, 22*(8), 3825. https://doi.org/10.3390/ijms22083825

Wu, H., Tong, L., Wang, Y., Yan, H., & Sun, Z. (2021). Bibliometric analysis of global research trends on ultrasound microbubble: A quickly developing field. *Frontiers in Pharmacology, 12*, 646626. https://doi.org/10.3389/fphar.2021.646626

Zhu, S., Li, L., Gu, Z., Chen, C., & Zhao, Y. (2020). 15 years of small: Research trends in nanosafety. *Small, 16*(36), 2000980. https://doi.org/10.1002/smll.202000980

Zhu, S., Liu, Y., Gu, Z., & Zhao, Y. (2021). A bibliometric analysis of advanced healthcare materials: Research trends of biomaterials in healthcare application. *Advanced Healthcare Materials, 10*(10), 2002222. https://doi.org/10.1002/adhm.202002222