Worldwide Publication Trends of Drug Repurposing and Drug Repositioning in the Science of Medicine (2003-2022)

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RESEARCH ARTICLE

Worldwide Publication Trends of Drug Repurposing and Drug Repositioning in the Science of Medicine (2003-2022)

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ABSTRACT:

Background: Science of medicine in the post-genomic era has significantly enhanced the knowledge of human diseases. These advancements could shed light to the trans 16 n of these benefits into drug therapeutics. Drug repurposing is a strategy that plays a pivotal role to provide novel insights into disease biology and further drive drug discovery as the ultimate goal. Herein, the current study aimed to analyse the global trends of drug repurposing peer-review publications from 2003 until 2022. **Methods:** We retrieved 1.371 articles related to drug repurposing studies and used similar terms and keywords, including "drug repositioning", "drug repurposing", "drug repurposing publications has increased drough at a drug recycling". **Results:** The number of drug repurposing publications has increased drough at a drug repurposing the United States, followed by China, India, the United Kingdom, and Italy, respectively. Meanwhile, the top five frequently used keywords are drug repurposing (n = 336), drug repositioning (n = 335), COVID-19 (n = 134), SARS-CoV-2 (n = 135), and molecular docking (n = 67). **Conclusions:** This study emphasizes the importance of conducting active research collaboration in drug repurposing and drug repositioning especially pertaining to the COVID-19 pandemic.

KEYWORDS: Drug repurposing, drug repositioning, drug discovery, drug reusing, molecular docking, bibliometric.

INTRODUCTION:

Developing new drugs from clinical trials to market is time-consuming and highly expensive in most therapeutic areas, estimated to be ~ 15 years and >US\$1 billion, respectively¹. More than 10.000 drugs undergoing clinical trials had been registered at www.clinicaltrials.gov, but only a few drug candidates made it to the next phase of clinical trials².

Received on 03.04.2022 Modified on 10.08.2022 Accepted on 13.11.2022 © RJPT All right reserved Research J. Pharm. and Tech 2023; 16(3):1333-1341. DOI: 10.52711/0974-360X.2023.00219 with around 5% of 13 ew molecules entering phase I clinical trial being approved by the United States of America (USA) Food and Drug Administration (FDA)³.

The dearth of these new clinically approved drugs has led to a new approach called drug repurposing as a promising strategy, which finds new uses for old drugs as usable therapeutic agents. Some advantages of drug repurposing are better understanding of drug safety, pharmacological mechanisms, and pharmacokinetic profiles⁴. Evidence revealed that old drugs are promisingly to be repurposed or reused for secondary indications⁵. Several examples of drug repurposing that

have been clinically used, including aspirin and sildenafil. Aspirin was initially used for pain relief and is currently used for cardiovascular disease prevention⁶. Sildenafil which was originally indicated to treat high blood pressure, was later repurposed for erectile dysfunction⁷. These examples emphases the promising insight of drug repurposing to identify new indications for various diseases treatments.

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The concept of drug repurposing also has been widely used for identifying new candidate drugs for the corona virus disease 2019 (COVID-19)8. Several drugs have been identified as emerging treatments of COVID-19 and recently are under clinical investigations, such as mesylate [NCT04524663]⁸, lopinavir [NCT04376814], oseltamivir [NCT04558463], and ritonavir [NCT04345276]9. The aforementioned reasons prove that drug repurposing has paved the way as a promising strategy to explore drug discovery faster, especially in the emerging pandemic. Drug repurposing is referred to use old drug for new indication 10, this term often interchangeable with the drug repositioning or drug reprofiling or drug reusing or drug recycling11. Every year, an increasing number of scientific publications related to the drug repurposing were published and the trend seems increasing dramatically. Therefore, it is of relevance to identify the trend of studies and publications related to the drug repurposing.

Bibliometric analysis has been a well method for quantitative evaluation of research articles including authors of each article, the journal where it was published, and the number of citations of these journals. The bibliometric analysis shed light the research activities through quantitative description of literature 12. Some of the bibliometric analysis were published in many areas of research, including schizophrenia¹³, malaria14 and cancers15,16. However, there were limited bibliometric analysis regarding the trend of drug repurposing and its similar terms. Therefore, the current study aims to evaluate and map the worldwide publications focused on the drug repurposing which were published through peer-review journals. Taken together, the ultimate goal of this study also provides the crucial information of the quantitative analysis of international publications related to drug repurposing and evaluates the research trend of drug repurposing publication mapping in each country.

Methods:

Study Design:

The current study used bibliometric analysis to identify the pattern and visualize the trend 12 drug repurposing studies worldwide. We also used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for identifying the searching

strategy and filtering the sources of the articles, as shown in the Supplementary Figure 1¹⁴. This study involved no human's participation; therefore, the review board approval was not a mandatory for conducting this study.

Data search and identification:

In this study, articles were obtained from the Scopus database accessed on 27/10/2021. Articles which were published from 2003 to 2022 are included in the data set for analysis. We excluded the articles that considered as proceedings, editorial materials, book chapters, abstract conferences, and reviews. Scopus database consists of many international peer-review, scientific journals with a high reputation for maintaining the quality of the articles. Therefore, this study data set was valid in representing the quality of the publication. We used some keywords and Bota an operator "OR" to gather the search, including Drug repositioning OR Drug repurposing OR Drug Reprofiling OR Drug reusing OR Drug recycling were applied to identify articles that matched this study objective.

Data extraction:

Peer-reviewed articles that are relevant to the keywords of this study were identified. The authors independently determined 1.371 articles to analyze their bibliometrics, and explored the relationships and research trends in the field of utilizing old drugs for the new indication.

Statistical analysis:

Bibliometric analysis is a method to analyze relevant literature through mathematic and statistic approaches and visualize to graphical representation of bibliometric maps. We used VOSViewer version 1.6.16 (Universiteit biden, The Netherland)¹⁷ dan Biblioshiny R package¹⁷ to build data matrices through individual bibliographic and to visualize the bibliometric networks based on citation, bibliographic coupling and conformity, and authorship relations.

RESULTS:

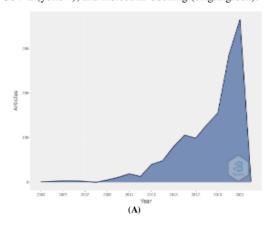
Total number of retrieved article and growth of drug repurposing publications:

We retrieved 2.292 articles which were published between 2003 to 2022. All articles were associated with drug repurposing and its synonym that often been used in the scientific field, including drug repositioning, drug reprofiling, drug reusing, and drug recycling. After extracting articles, we obtained 1.371 articles that met the inclusion criteria and 921 documents were excluded (Supplementary Figure 1).

According to the findings, the term "drug repurposing" came from an article published in the journal AIDS, with the title "Latino drug-recycling group distributes

hope in a bottle and an activist spirit" in 2003¹⁸. Based on this article, the term of drug-recycling was used as synonymous of drug repurposing term for the first time. While the term of drug repositioning in the original article started to be used in 2006. Li YY *et al.*, wrote the article with title "A large-scale computational approach to drug repositioning" which was applied in the computational approaches for identifying potential novel therapeutic by utilizing existing drugs for drug repositioning ¹⁹. Since 2006, the term of drug repositioning and drug repurposing have been commonly used in the scientific literatures and publications.

The annual number of publications with regards to drug repurposing in the early of 2000 until 2012 is less than 20 documents, and has been rising dramatically from early 2013 till 2022 (Figure 1A). While as depicted in the Figure 1B, upcoming topic research related to drug repurposing were visualized in Figure 1B. According to the network visualization by mapping the occurrence terms in the title, abstract and keywords, we therefore identified four clusters indicated five most-frequently used topics in the publications related to drug repurposing. The topics include drug repurposing (blue), drug repositioning (green), COVID-19 (yellow), SARS-CoV-2 (yellow), and molecular docking (bright green).



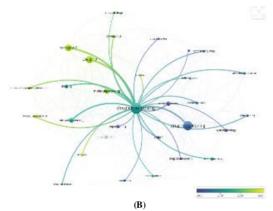


Figure 1. (A) Annual growth of drug repurposing publications. (B) Network visualisation map of author keywords in the drug repurposing literature (2003–2022). Topics include drug repurposing (blue), drug repositioning (green), COVID-19 (yellow), SARS-CoV-2 (yellow), and molecular docking (bright green).

Most cited documents related to drug repurposing:

From a total of 1.371 articles that met the eligibility, we highlighted top 10 articles with the highest citation, as shown in Table 1. Top two articles with the highest citation had been published in Nature (Impact Factor 2020 =49.962) and Cell Discovery (Impact Factor 2020 =10.849) journals, and these two articles were related with the COVID-19. The title of first highest citation was "A SARS-CoV-2 protein interaction map reveals targets for drug repurposing" with total amount of citations around 1.324 at the time of this article were published [20]. The second article with the title "Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2" reached a total amount of 642 citations on Nov26ber 2021 [21]. Among top 10 articles, we found that most of articles were published in the high impact factor journals and high-quality grades and they were listed in the Scimago Journal Rank (SJR) journal quartile one.

Table 1: Top 10 cited	publications in the field	of drug repurposing	research in 2003-2022

S. No	Publication Title	Year	Journal Name	Number of Citation*	Reference
1	A SARS-CoV-2 protein interaction map reveals targets for 2 lg repurposing	2020	Nature	1324	20
2	Network-based drug repurposing for novel coronavirus 2019- 17 V/SARS-CoV-2	2020	Cell Discovery	642	21
3	Discovery of drug mode of action and drug repositioning from 3 nscriptional responses	2010	PNAS	538	49
4	Prediction of drug-target interactions and drug repositioning network-based inference	2012	PLoS Computational Biology	530	50
5	Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen	2016	Nature Medicine	402	51

	1				
6	Repurposing of clinically developed drugs for treatment of	2014	Antimicrobial Agents	369	52
	2 ddle East respiratory syndrome coronavirus infection		and Chemotherapy		
7	Exploiting drug-disease relationships for computational drug	2011	Briefings in	311	53
	4 ositioning		Bioinformatics		
8	Consequences of treated water recycling as regards	2006	Environmental	257	54
	pharmaceuticals and drugs in surface and ground waters of a		Science and		
	3 dium-sized Mediterranean catchment		Technology		
9	A survey of current trends in computational drug repositioning	2016	Briefings in	255	55
	14		Bioinformatics		
10	Auranofin: Repurposing an Old Drug for a Golden New Age	2015	Drugs in R and D	245	56

^{*}Number of citations up to 2021

Country Collaboration related with the drug repurposing study:

It is important that the collaboration among authors for publishing scientific articles be encouraged especially in the academic field. The science will be widely beneficial especially when altogether done in large, collaborative teams. The collaboration entails communication, which indicated that the authors collaborate internationally to increase the benefit of sciences.

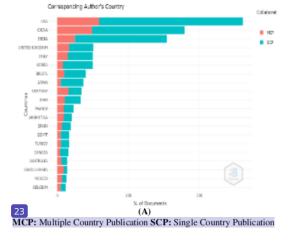
We analysed the single country collaboration (SCP) and multiple countries collaboration (MCP), resulting in top 5 countries subsequently with highest SCP and MCP, including USA, China, India, UK, and Italy (Figure 2A and 2B). The United States published 261 articles (59 MCP; 202 SCP), followed by China with 179 publications (49 MCP; 130 SCP). India published 154 articles (25 MCP; 129 SCP), the United Kingdom published 51 articles (17 MCP and 34 SCP), and the last country, Italy, published 50 articles (15 MCP; 34 SCP) (Table 2).

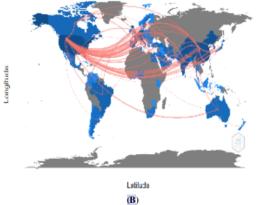
Table 2. Countries with highest active collaboration related to drug repurposing publications from 2003 to 10 22

Country	Article	Frequency	SC	P MCP	MCP
					Ratio
USA	261	0.218045	202	59	0.22
CHINA	179	0.149541	130) 49	0.27
INDIA	154	0.128655	129	25	0.16
UNITED	51	0.042607	34	17	0.33
KINGDOM					
ITALY	50	0.041771	35	15	0.30
KOREA	50	0.041771	42	8	0.16
BRAZIL	40	0.033417	30	10	0.25
JAPAN	37	0.030911	32	5	0.13
GERMANY	34	0.028404	18	16	0.47
IRAN	33	0.027569	22	11	0.33
FRANCE	23	0.019215	14	9	0.39
ARGENTINA	21	0.017544	12	9	0.42
SPAIN	19	0.015873	12	7	0.36
EGYPT	17	0.014202	12	5	0.29
TURKEY	17	0.014202	12	5	0.29
CANADA	16	0.013367	12	4	0.25
AUSTRALIA	14	0.011696	8	6	0.42
SAUDI	14	0.011696	5	9	0,64
ARABIA					
MEXICO	13	0.010860	6	7	0.53
36 ELGIUM	12	0.010025	7	5	0.41
SCP; Single C	Country 1	Publication,	MCP;	Multiple	Countries

Publication

Figure 2. Countries with active collaboration in drug repurposing research from 2003 through 2022. (A) Most active, collaborative countries and their international collaboration 28 n drug repurposing research, presented by SCP and MCP. (SCP; Single Country Publication, MCP; Multiple Countries Publication). (B) Frequency of research collaboration among countries related to drug repurposing studies,





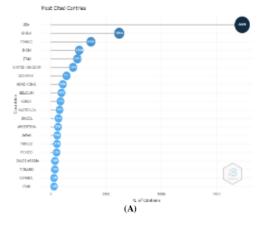
Analysis of country collaborations (SCP and MCP) are beneficial as alternative information for researchers, especially new researchers to determine international research networks. The detailed frequency of each country in their collaboration with other countries is depicted in Table 3. It shows that the USA and China collaborated in research 55 times -- it was considered as the most active country collaboration, the 31 llowed by 30 times research collaboration between USA and the UK. Indicated the number of collaborations among authors between two countries (USA-China) was higher than that of two other countries (USA-UK).

Table 3. The most active countries and their international collaborators

Country Name	Collaborator	Frequency
USA	China	55
USA	United kingdom	30
UNITED KINGDOM	Belgium	14
USA	Germany	14
USA	France	13
USA	India	13
UNITED KINGDOM	Germany	12
USA	Belgium	12
CHINA	Hong kong	11
USA	Canada	10
SAUDI ARABIA	Pakistan	8
UNITED KINGDOM	Italy	8
CHINA	United kingdom	7
USA	Switzerland	7
CHINA	Singapore	6
INDIA	Germany	6
INDIA	Saudi arabia	6
USA	Australia	6

Geographical distribution of drug repurposing mong countries:

The geographical distribution of the retrieved documents is presented in Figure 3. Publications in the field of drug repurposing were vary across countries, resulted that drug repurposing research and publication was led by the USA. In addition, the USA was considered as the country with the highest citation countries (Figure 3A). Instead of the highest number of publications, it is shown that India is more actively involved in conducting research collaboration with other countries than the USA in 2021, as shown with yellow colour in Figure 3B.



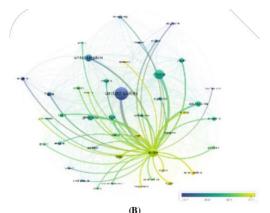


Figure 3. (A). Most cited countries related to drug repurposing publications (B). Network visualisation map of drug repurposing research (2003–2022); top 5 active countries in publishing drug repurposing research

The trend of using keywords related to drug repurposing

Keywords are the comerstone to search intended studies in various databases. One aim of using appropriate keywords is to help researchers obtain articles that are related to the topic of their study [22]. It means that appropriate [22] words are essential to gather relevant information in the field of drug repurposing. The popular keywords of drug repurposing publication and drug repurposing related to the current field is presented in Table 4.

Table 4. The most-frequently used keywords in drug repurposing publications

Terms	Frequency
Drug repurposing	336
Drug repositioning	235
COVID-19	134
SARS-CoV-2	115
Molecular docking	67
Virtual screening	54
Repurposing	48
Drug discovery	46
Docking	34
Molecular dynamics	25
Repositioning	24
Machine learning	23
Systems biology	23
Cancer	21
Bioinformatics	19
Coronavirus	19
Molecular dynamics simulation	16
Alzheimer's disease	15
Data mining	14
Drug development	14
Inflammation	14
Breast cancer	13
Connectivity map	13
In silico	13
Antiviral drugs	12

According to this analysis, we respectively determined that the most popular keywords are drug repurposing (n=336), drug repositioning (235), COVID-19 (n=134), SARS-CoV2 (n=115), and molecular docking (n=67) (Figure 4A and 4B).

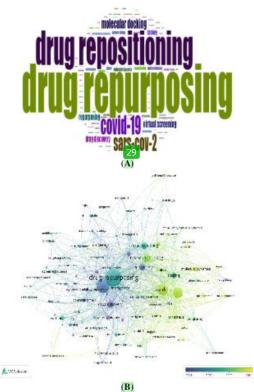


Figure 4. (A) Word cloud analysis of the most used keywords in drug repurposing publications (B) Overlay visualization of drug repurposing research related with the current field. Bigger blot represents higher number of publications.

DISCUSSION:

Drug repurposing and drug repositioning are two similar concepts of using old drug for a new indication 11. These two terms have been a trend in the science medicine literatures since 2003. No articles regarding drug repurposing were found before 2003. Number of articles have begun to escalate since 2003 and reached its peak in 2020. Drug repurposing in science of medicine growing rapidly through utilizing several approaches such as molecular docking for various diseases23-27 and data mining-based approach28. Besides, it has been assumed that the peak of published articles might be particularly associated with abundant clinical studies to find new drug candidate for the COVID-19. The purpose of recent study was to identify the trends of drug repurposing publication worldwide. To achieve our aim. we used bibliometric analysis using selected keywords,

country publication related to drug repurposing, including countries with the most productive in drug repurposing researches, as well as the annual number of publications.

The result of current study leads to significant insights related to drug repurposing publications. We identified the trend of drug repurposing publications have elevated dramatically egry year, particularly from a period of 2013 to 2020 with the highest number of publications was attained in 2020. It is surprising that in the early of 2020 the COVID-19 outbreak pandemic was confirmed and it was becoming a major international concern related with impacted the global health status²⁹. These pandemic leads scientists to focus finding, exploring, and developing drugs against the SARS-CoV-230. Due to these reasons, the pattern of publication related to drug repurposing in 2020 was prominent concern on utilizing old drug as a new indication for the COVID-19 treatment. In addition, the findings presented the trend of using drug repurposing approach to identify new drug against the COVID-19. The COVID-19 pandemic has not yet alleviated as no recent specific medications are available. When this occurs continuously, the situation can become worse including to mental health31,32. It is currently still under clinical investigation and conventional repositioned drugs an alternative treatment of COVID-1933. According to the visualization in Figure 4, we noticed that the drug repurposing was not only related to the COVID-19, but also some other target proteins have been identified, such as TMPRSS234, ACE-235, ph33 chemical Inhibitors 36 and antibiotic drugs against the papain like protease of SARS-CoV-2 ³⁷. Some other drugs are still under clinical investigation, including ivermectin 38, 39 and remdesivir, the latter has been approved to be an emergency treatment against the COVID-19 [40]. This recent finding emphasized that drug repurposing-based approach has been widely used for identifying new candidate drug for treatment of the COVID-19.

The USA is considered as the country with the highest citation that contributed to the field of drug repurposing research. Potential reasons might be influenced by the USA active international collaboration in research and science. In addition, the USA leads fundamental medical research or experimental trials worldwide, supported by abundant funds and resources, policies, advanced tech 25 bgies, and high-qualified researchers 41. In fact, two articles with the highest number of citations were published in *Nature* and *Cell Discovery* in 2020, and these two articles were objec 32 ly exploring the candidates of new drug for the COVID-19 treatment 2021. There is still an urgent need of finding new drugs and utilizing old drug against COVID-19 might be considered as an alternative so far that primary treatment

is currently symptomatic⁴². Most of publishers intended to call researchers to publish their research regarding the new drug discovery against the SARS-CoV-2, and provide them free access in the special issues ⁴³.

Our analysis revealed that USA was not only the most active country in the publication of drug repurposing studies, but also the most frequent country with international collaboration. International collaboration is highly recommended for advance science and its implementation throughout the world ^{44, 45}. As revealed by Savage et al., (2018), collaboration is the key of cancer research, nowadays finding the new drug candidate to combat the COVID-19 is an emerging issue ^{43,46}. All scientists are in a rush to synergize together in the involvement of the COVID-19 Collaboration is not only enhancing productivity of researchers but also can accelerate the output of finding. Several funding schemes has been provided by the international institutions to link research groups across countries 47,48.

STRENGTH AND LIMITATIONS:

Bibliometric visual analysis for drug repurposing provides an insight driven drug discovery for the COVID-19 treatment. Current citation and upcoming topics showed that the drug repurposing was reliable for identifying new drug candidate against COVID-19. Our bibliometric analysis used Scopus database. Although Scopus database is one of the largest databases in scientific field and provides high validity of each article, however, this study still has some limitations, such as bias toward English journals, publications from several developing countries that might published in non-English, and the journals that not indexed in Scopus.

IMPLICATION AND FURTHER STUDY:

This bibliometric analysis only represents the initial phase of drug repurposing study, nevertheless this study may bring a new light on the paramount progress of drug repulsioning research, especially the drug discovery for the COVID-19 treatment. A systematic review and meta-analysis of randomized clinical trials that implement 35 old drugs against COVID-19 is highly needed to provide important information to the healthcare providers and stakeholders in the clinical practice.

CONCLUSION:

Drug repurposing has been widely used in discovering and developing new drugs for emerging diseases. It reminds signal of the continuing research development. We concluded that the most active country in collabor of gresearch worldwide and publishing articles reached the highest number of citations in the field of drug repurposing. The USA actively and aggressively

conducting research using drug repurposing approach to combat the COVID-19 pandemic. It is foreseeable that drug repurposing approach could be further explored to find new therapeutic agents and it is presumably implemented for further outbreak in the clinical practices.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE:

No ethical approval was required, as this was a bibliometric review for the existing literature.

AVAILABILITY OF DATA AND MATERIALS:

This study analysed the dataset from publicly available dataset. The source of this study can be accessed here https://www.scopus.com/results

COMPETING INTERESTS:

The authors disclose no conflict



AUTHORS' CONTRIBUTIONS:

LMI and ZN conceived and designed the study. LMI and ZN performed all data analyses. LMI, ZN, DAP, YRN, WA, HD, RM, MAS and 20 C interpreted the results and revised the paper. LMI wrote the manuscript. All authors read and approved the final manuscript.

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