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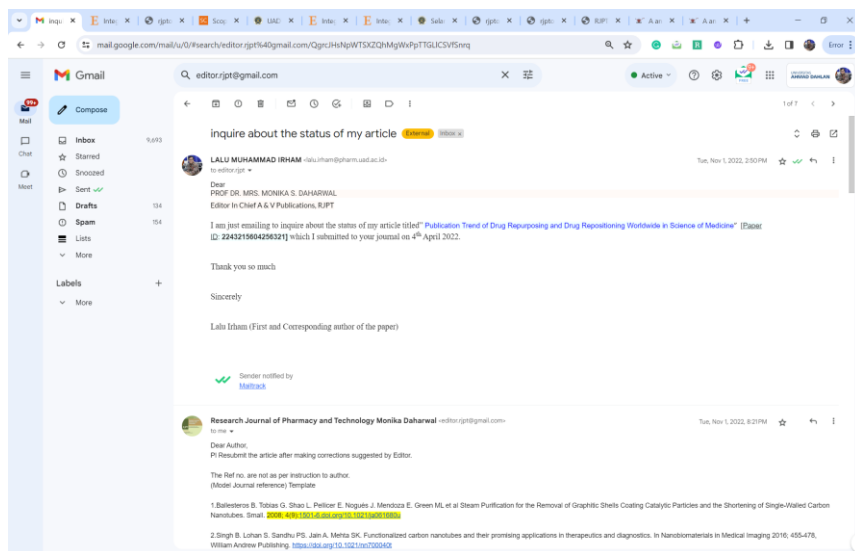
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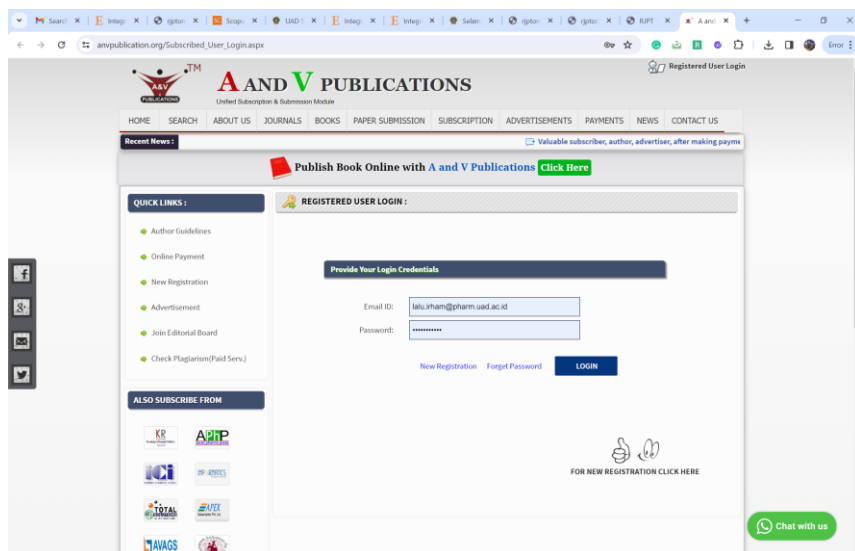
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Research Journal of Pharmacy and Technology

Paper ID: **2243215604256321**   Date of Submission: **03-Apr-2022**

Paper Title: **Publication Trend of Drug Repurposing and Drug Repositioning Worldwide in Science of Medicine**

Authors: **Lalu Muhammad Irham;Zalik Nuryana;Dyah Aryani Perwitasari;Yudha Rizky Nuari; Made Ary Sarasmita; Wirawan Adikusuma;Haafizah Dania; Rita Maliza;Rocky Cheung**

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2.Singh B. Lohan S. Sandhu PS. Jain A. Mehta SK. Functionalized carbon nanotubes and their promising applications in therapeutics and diagnostics. In Nanobiomaterials in Medical Imaging 2016; 455-478. William Andrew Publishing. https://doi.org/10.1021/nn700040t

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 This manuscript only requires minor revision from me because the research concept and analysis of the results are already good. There are several references that need to be updated in this manuscript to improve the quality of the manuscript. I have written detailed comments from me in the manuscript (attached).

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Dear Editors,

Please find our attached manuscript entitled "**Publication Trend of Drug Repurposing and Drug Repositioning Worldwide in Science of Medicine (2003-2022)**" which we are submitting for consideration for publication as an Original Research article in Research Journal of Pharmacy and Technology (**Paper ID:2243215604256321**). We are thankful for your kind suggestions regarding our manuscript. Here, we are sending our revised manuscript in accordance with the comments given by the reviewers and the editors. We have read through all the reviewers' suggestions very carefully, and made the necessary revisions based on these comments, as detailed below in a point-by-point format. The revised sections are highlighted in yellow. Finally, we would like to thank you once again for giving us the opportunity to improve our manuscript. We very much hope that these revisions are adequate. We appreciate your assistance and are looking forward to hearing from you.

Sincerely yours,

Apt Lalu Muhammad Irham M.Farm..,Ph.D

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Universitas Ahmad Dahlan, Yogyakarta, Indonesia
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Kec. Umbulharjo, Kota Yogyakarta, Daerah Istimewa Yogyakarta. Indonesia

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2.Singh B. Lohan S. Sandhu PS. Jain A. Mehta SK. Functionalized carbon nanotubes and their promising applications in therapeutics and diagnostics. In Nanobiomaterials in Medical Imaging 2016; 455-478, William Andrew Publishing. https://doi.org/10.1021/nn700040t

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

Lalu Muhammad Irham[1*]., Zalik Nuryana[2]., Dyah Aryani Perwitasari[1].,Yudha Rizky Nuari[1].,Made Ary Sarasmita[5,6].,Wirawan Adikusuma[3]., Haafizah Dania[1]., Rita Maliza[4].,Rocky Cheung[7]

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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 translation 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 reprofiling", "drug reusing", and "drug recycling".

Results: The number of drug repurposing publications has increased dramatically from 2003 through 2022. Besides, the most active country in publishing drug repurposing research is 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, respectively [1]. 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 trials [2], with around 5% of new 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 profiles [4]. Evidence revealed that old drugs are promisingly to be repurposed or reused for secondary indications [5]. 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 prevention [6]. Sildenafil which was originally indicated to treat high blood pressure, was later repurposed for erectile dysfunction [7]. These examples emphases the promising insight of drug repurposing to identify new indications for various diseases treatments.

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 camostat 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 recycling [11]. 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 schizophrenia [13], malaria [14] and cancers [15, 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 of 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 1[14]. 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 Boolean 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 the graphical representation of bibliometric maps. We used VOSViewer version 1.6.16 (Universiteit Leiden, The Netherland) [17] dan Biblioshiny R package [17] to build data matrices through individual bibliographic and to visualize the bibliometric networks based on citation, bibliographic coupling and conformity, and authorship relations.
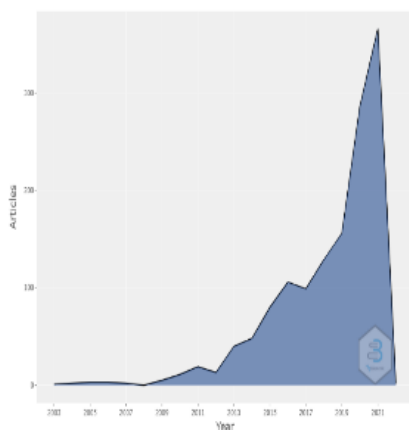
Results

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 2003 [18]. 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).

(A) (B)

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).
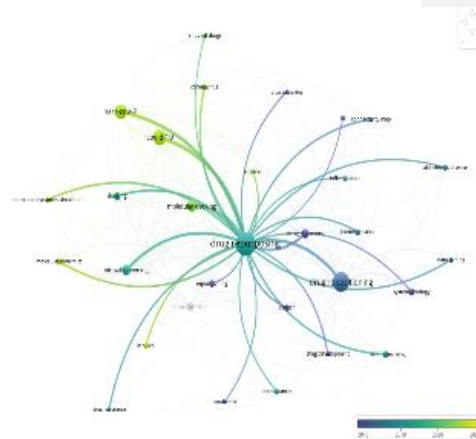
Most cited documents related to drug repurposing

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 November 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

No	Publication Title	Year	Journal Name	Number of Citation[*]	Reference
1	A SARS-CoV-2 protein interaction map reveals targets for drug repurposing	2020	Nature	1324	[20]
2	Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2	2020	Cell Discovery	642	[21]
3	Discovery of drug mode of action and drug repositioning from transcriptional responses	2010	PNAS	538	[49]
4	Prediction of drug-target interactions and drug repositioning via 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]
6	Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection	2014	Antimicrobial Agents and Chemotherapy	369	[52]
7	Exploiting drug-disease relationships for computational drug repositioning	2011	Briefings in Bioinformatics	311	[53]
8	Consequences of treated water recycling as regards pharmaceuticals and drugs in surface and ground waters of a medium-sized Mediterranean catchment	2006	Environmental Science and Technology	257	[54]
9	A survey of current trends in computational drug repositioning	2016	Briefings in Bioinformatics	255	[55]
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 2022

Country	Article	Frequency	SCP	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 KINGDOM	51	0.042607	34	17	0.33
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

(A)

SAUDI ARABIA	14	0.011696	5	9	0,64
MEXICO	13	0.010860	6	7	0.53
BELGIUM	12	0.010025	7	5	0.41

SCP; Single Country Publication, MCP; Multiple Countries Publication

(A)   (B)

MCP: Multiple Country Publication   **SCP:** Single Country Publication

Figure 2. Countries with active collaboration in drug repurposing research from 2003 through 2022. (**A**) Most active, collaborative countries and their international collaborations in 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, then followed 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 among 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 as compared to other 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**.
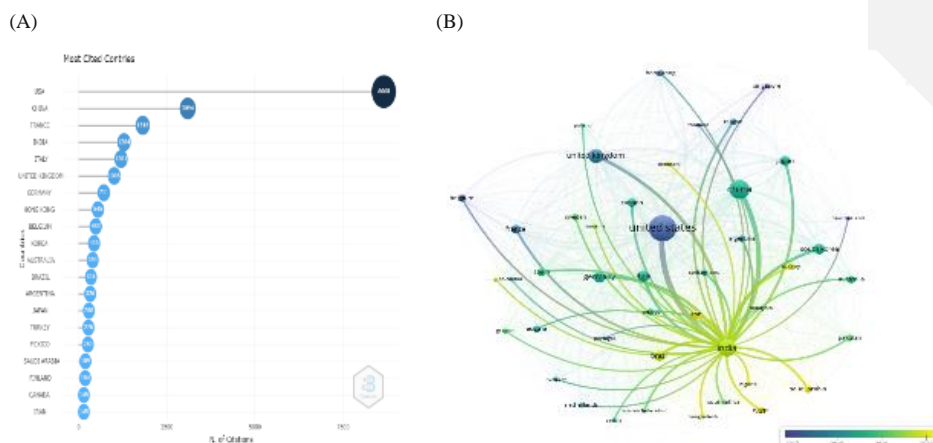
(A)

(B)

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 cornerstone 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 keywords 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**).
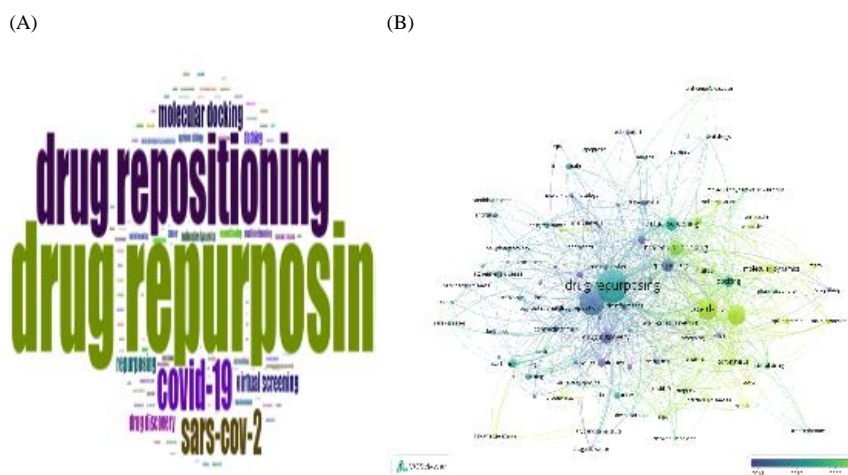
(A)   (B)

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 diseases [23-27] and data mining-based approach[28]. 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 every 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 status [29]. These pandemic leads scientists to focus finding, exploring, and developing drugs against the SARS-CoV-2[30]. 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 health[31, 32]. It is currently still under clinical investigation and conventional repositioned drugs an alternative treatment of COVID-19 [33]. 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 TMPRSS2 [34], ACE-2 [35], phytochemical 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 technologies, 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 objectively exploring the candidates of new drug for the COVID-19 treatment [20, 21]. 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 symptomatic[42]. 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 research. 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 repurposing research, especially the drug discovery for the COVID-19 treatment. A systematic review and meta-analysis of randomized clinical trials that implemented 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 collaborating research 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.

Acknowledgment
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Additional File
Supplementary Figure 1

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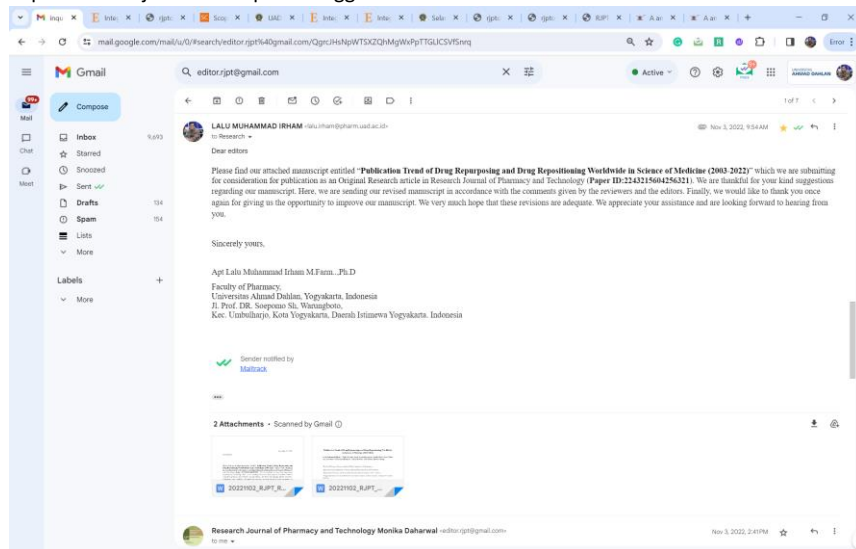
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Publication Trend of Drug Repurposing and Drug Repositioning Worldwide in Science of Medicine (2003-2022)

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ABSTRACT:

Background: Advanced science of medicine in the post-genomic era nowadays enhanced the knowledge of human diseases. These advancements could be shed light to translate these benefits into therapeutic. Drug repurposing is one of the strategies will be pivotal role for providing novel insights into disease biology and further driven drug discovery as an ultimate aim. Herein, the current study aimed to analyse the research trend of drug repurposing peer-review publications globally from 2003 until 2022.

Methods: We retrieved 1371 articles related to drug repurposing studies and we used similar terms using keywords, including "drug repositioning", "drug repurposing", "drug reprofiling", "drug reusing", and "drug recycling".

Results: Our finding highlighted that the trend of drug repurposing publications had been increased dramatically since 2003 to 2022. Besides, the most active country in publishing drug repurposing research was the United State followed by China, India, the United Kingdom, and Italy, respectively. Meanwhile, top five frequently used keywords were 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 regarding to the current situation of the COVID-19 pandemic.

KEYWORDS: Drug repurposing, Drug repositioning, Drug discovery, Molecular docking, Bibliometric.

INTRODUCTION:

Developing new drugs from the clinical trials to the market is time-consuming and highly expensive in some therapeutic areas, estimated to be ∼15 years and >US$1 billion respectively [47]. It is more than 10,000 drugs under clinical trials had been registered at www.clinicaltrials.gov, but only a few drug candidates made it to the next phase of clinical trials [22], with around 5% of new molecules entering phase I clinical trial being approved by the United States (US) Food and Drug Administration (FDA) [35]. The dearth of these new clinical approved drugs has led to a new approach called drug repurposing as a promising strategy which concerns of finding new uses for old drugs as useable therapeutic agents. Some advantages of drug repurposing are better understanding of drug safety, pharmacological mechanisms, and pharmacokinetic profiles [7]. Evidences revealed that around 90% of old drugs are promisingly to be repurposed or reused for secondary indications [17]. 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 prevention [4,54]. Sildenafil which was originally indicated to treat high blood pressure, was later repurposed for erectile dysfunction [18]. These examples emphases the promising insight of drug repurposing to identify new indications for various diseases treatments.

The concept of drug repurposing also has been widely used for identifying new candidate drugs for the corona virus disease 2019 (COVID-19) [46]. Several drugs have been identified as an emerging treatments of COVID-19 and recently are under clinical investigations, such as camostat mesylate [NCT04524663] [46], lopinavir [NCT04376814], oseltamivir [NCT04558463], and ritonavir [NCT04345276] [31]. 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 [37], this term often interchangeable with the drug repositioning or drug reprofiling or drug reusing or drug recycling [28]. Every year, increasing number of scientific publications related to the drug repurposing were published and the trend seems

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Writing references please use the help of a reference manager such as Mendeley, EndNote, etc

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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 [27]. Some of the bibliometric analysis were published in many areas of research, including schizophrenia [33], malaria [48] and cancers [52,55]. 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 evaluate the research trend of drug repurposing publication mapping in each country.

MATERIALS AND METHODS:

Study Design

The current study used bibliometric analysis to identify the pattern and visualize the trend of 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 1[14]. 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, which was accessed on 27/10/2021. Articles which published since 2003 to 2022, had been included in the data set. 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 Boolean 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.

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Data extraction

Peer-reviewed articles that relevant to the keywords of this study were identified. The authors independently determined 1371 articles to analyse their bibliometric and explored the relationships and research trends in the field of utilizing old drugs for the new indication.

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Statistical analysis

Bibliometric analysis is a method to analyze relevant literature through mathematic and statistic approaches and visualize the graphical representation of bibliometric maps. We used VOSViewer version 1.6.16 (Universiteit Leiden, The Netherland) [17] dan Biblioshiny R package [6] to build data matrices through individual bibliographic and to visualize the bibliometric networks based on citation, bibliographic coupling and conformiting, and authorship relations.

RESULTS:

Total number of retrieved article and growth of drug repurposing publications

We retrieved 2292 articles which had been published since 2003 to 2022. All articles were associated with drug repurposing and its synonym (similar terms) that often been used in the scientific field, including drug repositioning, drug reprofiling, drug reusing, and drug recycling. After extracting articles, we obtained 1371 articles that met our inclusion criteria and 921 documents were excluded (Supplementary Figure 1).

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According to the findings, it is noted that the drug repurposing term used in scientific field that came from one article that published in the journal AIDS with the title "Latino drug-recycling group distributes hope in a bottle and an activist spirit" in 2003 [9]. 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

[30]. 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 regard to drug repurposing in the early of 2000 until 2012 was less than 20 documents and has been rising up dramatically from early 2013 up to 2022 (Figure 1A). It seems to be increased in the coming year. While as depicted in 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 colour), drug repositioning (green colour), COVID-19 (yellow colour), SARS-COV-2 (yellow colour), and molecular docking (bright green colour).
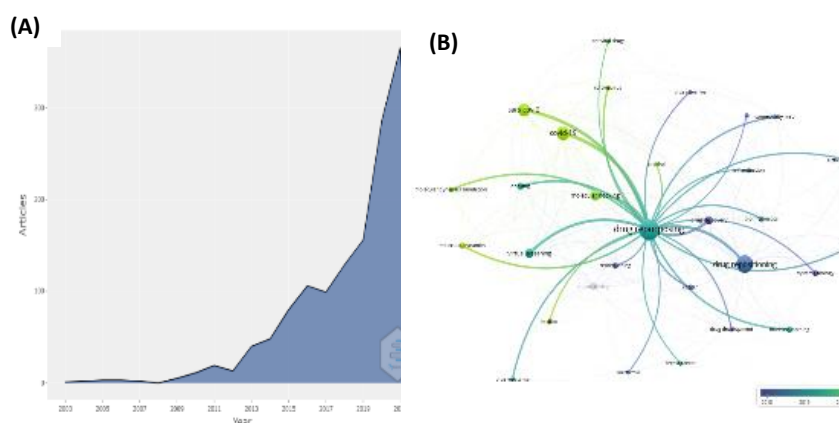

Figure 1. (A) Annual growth of drug repurposing publications. (B) Network visualisation map of author keywords of drug repurposing literatures (2003–2022).

Most cited documents related with drug repurposing

From a total of 1371 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* (IF 2020 =49.962) and *Cell discovery* (IF 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 1324 at the time of this article were published [19]. 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 10 November 2021 [58]. 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

No	Publication Title	Year	Journal Name	Number of Citation[*]	Reference
1	A SARS-CoV-2 protein interaction map reveals targets for drug repurposing	2020	Nature	1324	[16]
2	Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2	2020	Cell Discovery	642	[46]
3	Discovery of drug mode of action and drug repositioning from transcriptional responses	2010	PNAS	538	[21]
4	Prediction of drug-target interactions and drug repositioning via network-based inference	2012	PLoS Computational Biology	530	[10]
5	Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen	2016	Nature Medicine	402	[45]
6	Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection	2014	Antimicrobial Agents and Chemotherapy	369	[13]

7	Exploiting drug-disease relationships for computational drug repositioning	2011	Briefings in Bioinformatics	311	[12]
8	Consequences of treated water recycling as regards pharmaceuticals and drugs in surface and ground waters of a medium-sized Mediterranean catchment	2006	Environmental Science and Technology	257	[32]
9	A survey of current trends in computational drug repositioning	2016	Briefings in Bioinformatics	255	[25]
10	Auranofin: Repurposing an Old Drug for a Golden New Age	2015	Drugs in R and D	245	[33]

Country Collaboration related with the drug repurposing study

It is important that the collaboration among authors for publishing scientific articles should be encouraged especially in the academic field. The science will be widely beneficial when altogether done in large team [56]. The collaboration meaning of communication, it is indicated that the authors collaborate internationally to increase the benefit of sciences.

Herein, we analysed the single country collaboration (SCP) and multiple countries collaboration (MCP), resulted that top 5 countries subsequently altogether 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 2022

Country	Article	Freq	SCP	MCP	MCP Ratio
USA	261	0,218045	202	59	0,226
CHINA	179	0,149541	130	49	0,274
INDIA	154	0,128655	129	25	0,162
UNITED KINGDOM	51	0,042607	34	17	0,333
ITALY	50	0,041771	35	15	0,3
KOREA	50	0,041771	42	8	0,16
BRAZIL	40	0,033417	30	10	0,25
JAPAN	37	0,030911	32	5	0,135
GERMANY	34	0,028404	18	16	0,471
IRAN	33	0,027569	22	11	0,333
FRANCE	23	0,019215	14	9	0,391
ARGENTINA	21	0,017544	12	9	0,429
SPAIN	19	0,015873	12	7	0,368
EGYPT	17	0,014202	12	5	0,294
TURKEY	17	0,014202	12	5	0,294
CANADA	16	0,013367	12	4	0,25
AUSTRALIA	14	0,011696	8	6	0,429
SAUDI ARABIA	14	0,011696	5	9	0,643
MEXICO	13	0,01086	6	7	0,538
BELGIUM	12	0,010025	7	5	0,417

SCP; Single Country Publication, MCP; Multiple Countries Publication

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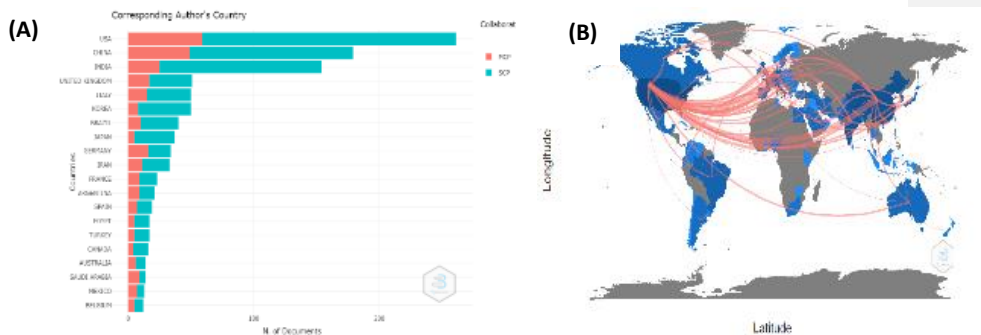
MCP: Multiple Country Publication
SCP: Single Country Publication

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

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

Table 3. Top 20 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 among countries

The geographical distribution of the retrieved documents was 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 US. In addition, the US was considered as the highest citation country compared to other 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 US in 2021, as shown with yellow colour in Figure 3B.

(A)

(B)

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

The keywords are the cornerstone to search intended studies in various databases. One aim of using appropriate keywords is to help researchers in obtaining articles that related to the topic of their study [20]. It means that appropriate keywords are essential to gather relevant information in the field of drug repurposing. The popular keywords of drug repurposing publication and drug repurposing related to current field was presented in Figure 4. According to this analysis, we respectively determined that the most popular keywords were drug repurposing (n=336), drug repositioning (235), Covid-19 (n=134), SARS-Cov2 (n=115), and molecular docking (n=67) (Figure 4A and 4B).

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

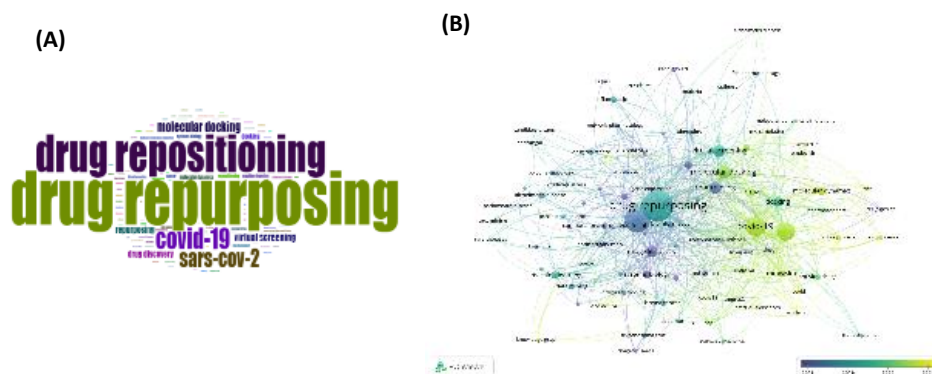| Terms	Frequency
Drug repurposing	336
Drug repositioning	235
COVID-19	134
SARS-COV-2	115
Molecular docking	67
Virtual screening	54
Repurposing	48
Drug discovery	46
Docking	34
Molecular dynamics	25
Repositioning	24
Machine learning	23
Systems biology	23
Cancer	21
Bioinformatics	19
Coronavirus	19
Molecular 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

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 [28]. 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 diseases [8,26,32,39,40] and data mining-based approach [5]. 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 determined significant insights related to the drug repurposing publication. We identified the trend of drug repurposing publications have elevated dramatically every 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 status [23]. These pandemic leads scientists to focus finding, exploring, and developing drugs against the SARS-COV-2[3]. 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 health[44,45]. it is currently still under clinical investigation and conventional repositioned drugs an alternative of COVID-19 [14]. 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 TMPRSS2 [25], ACE-2 [21], phytochemical Inhibitors[36] and antibiotic drugs against the papain like protease of SARS-CoV-2 [51]. Some other drugs are still under clinical investigation, including ivermectin [11,34] and remdesivir, the latter has been approved to be an emergency treatment against the COVID-19 [10]. 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 US has been considered as the country with the highest citation that contributed to the field of drug repurposing research. Potential reason might be influenced by the US active international collaboration in research and science. In addition, the US leads fundamental medical research or experimental trials worldwide, supported by abundant funds and resources, policies, advanced technologies, and high-qualified researchers [49]. In fact, two articles with the highest number of citations were published in *Nature* and *Cell discovery* in 2020, and these two articles were objectively exploring the candidate of new drug for the COVID-19 treatment [19,58]. There is still urgent need of finding new drugs and utilizing old drug against COVID-19 might be considered as an alternative so far taht primary treatment is currently symptomatic [42]. Most of publishers

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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 [1].

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 [12,50]. 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 [1,43]. All scientists are in a rush to synergize together in the involvement of the COVID-19 research. 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 [2,53].

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 repurposing research, especially the drug discovery for the COVID-19 treatment. A systematic review and meta-analysis of randomized clinical trials that implemented 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 collaborating research worldwide and publishing articles reached the highest number of citations in the field of drug repurposing. The US 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.

ETHIC APPROVAL:
No ethical approval for human participants 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

CONFLICT OF INTEREST:
The authors disclose no conflict of interest.

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

ADDITIONAL FILE:
Supplementary Figure 1

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With reference to your article titled **'Publication Trend of Drug Repurposing and Drug Repositioning Worldwide in Science of Medicine'** Author by **Lalu Muhammad Irham, Zalik Nuryana, Dyah Aryani Perwitasari, Yudha Rizky Nuari, Made Ary Sarasmita, Wirawan Adikusuma, Haafizah Dania, Rita Maliza, Rocky Cheung**. We wish to bring to your kind notice the following:

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Thanking you for submission of manuscript.

Yours sincerly.

Editor in Chief

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 translation 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 reprofiling", "drug reusing", and "drug recycling". **Results:** The number of drug repurposing publications has increased dramatically from 2003 through 2022. Besides, the most active country in publishing drug repurposing research is 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, respectively[1]. 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 trials[2].

with around 5% of new 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 profiles[4]. Evidence revealed that old drugs are promisingly to be repurposed or reused for secondary indications[5]. 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 prevention[6]. Sildenafil which was originally indicated to treat high blood pressure, was later repurposed for erectile dysfunction[7]. These examples emphases the promising insight of drug repurposing to identify new indications for various diseases treatments.

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 camostat 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 recycling[11]. 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 schizophrenia[13], malaria[14] and cancers[15,16]. 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 of 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 1[14]. 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 Boolean 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 the graphical representation of bibliometric maps. We used VOSViewer version 1.6.16 (Universiteit Leiden, The Netherland)[17] dan Biblioshiny R package[17] 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 2003[18]. 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).
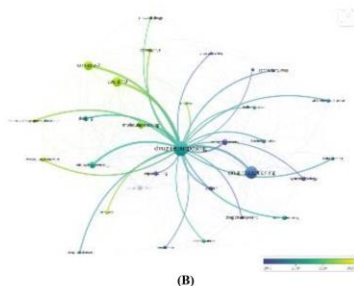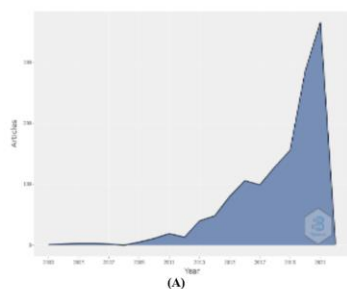

(B)

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 November 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.

(A)

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 drug repurposing	2020	Nature	1324	20
2	Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2	2020	Cell Discovery	642	21
3	Discovery of drug mode of action and drug repositioning from transcriptional responses	2010	PNAS	538	49
4	Prediction of drug-target interactions and drug repositioning via 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

1335

6	Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection	2014	Antimicrobial Agents and Chemotherapy	369	52
7	Exploiting drug-disease relationships for computational drug repositioning	2011	Briefings in Bioinformatics	311	53
8	Consequences of treated water recycling as regards pharmaceuticals and drugs in surface and ground waters of a medium-sized Mediterranean catchment	2006	Environmental Science and Technology	257	54
9	A survey of current trends in computational drug repositioning	2016	Briefings in Bioinformatics	255	55
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

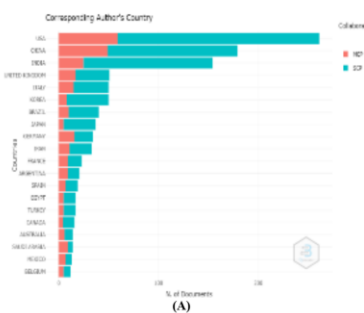## Country Collaboration related with the drug repurposing study:

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 2022

Country	Article	Frequency	SCP	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 KINGDOM	51	0.042607	34	17	0.33
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 ARABIA	14	0.011696	5	9	0.64
MEXICO	13	0.010860	6	7	0.53
BELGIUM	12	0.010025	7	5	0.41

SCP; Single Country Publication, MCP; Multiple Countries Publication

(A)

MCP: Multiple Country Publication **SCP:** Single Country Publication
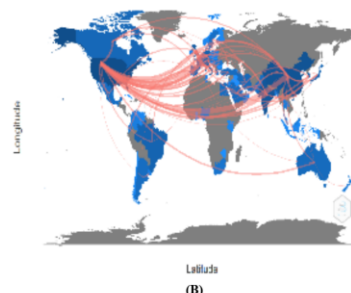

(B)

Figure 2. Countries with active collaboration in drug repurposing research from 2003 through 2022. (A) Most active, collaborative countries and their international collaborations in 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, then followed 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 among 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 as compared to other 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.
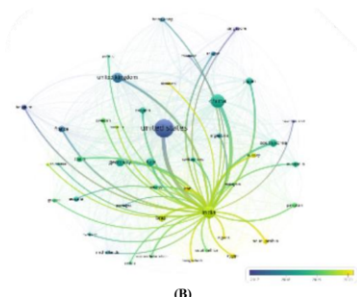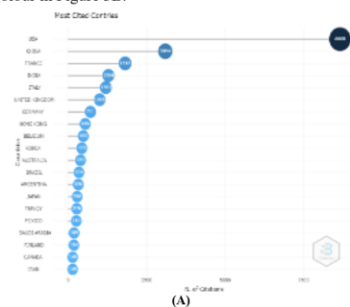
(A)

(B)

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 cornerstone 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 keywords 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).
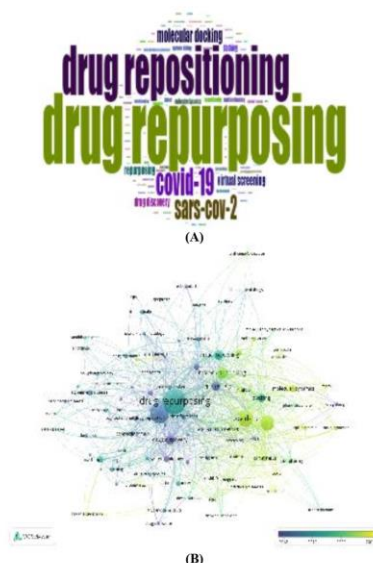

(A)

(B)

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 diseases[23-27] and data mining-based approach[28]. 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 every 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 status[29]. These pandemic leads scientists to focus finding, exploring, and developing drugs against the SARS-CoV-2[30]. 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 health[31,32]. It is currently still under clinical investigation and conventional repositioned drugs an alternative treatment of COVID-19[33]. 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 TMPRSS2[34], ACE-235, phytochemical 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 technologies, 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 objectively exploring the candidates of new drug for the COVID-19 treatment [20,21]. 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 symptomatic[42]. 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 research. 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 repurposing research, especially the drug discovery for the COVID-19 treatment. A systematic review and meta-analysis of randomized clinical trials that implemented 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 collaborating research 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
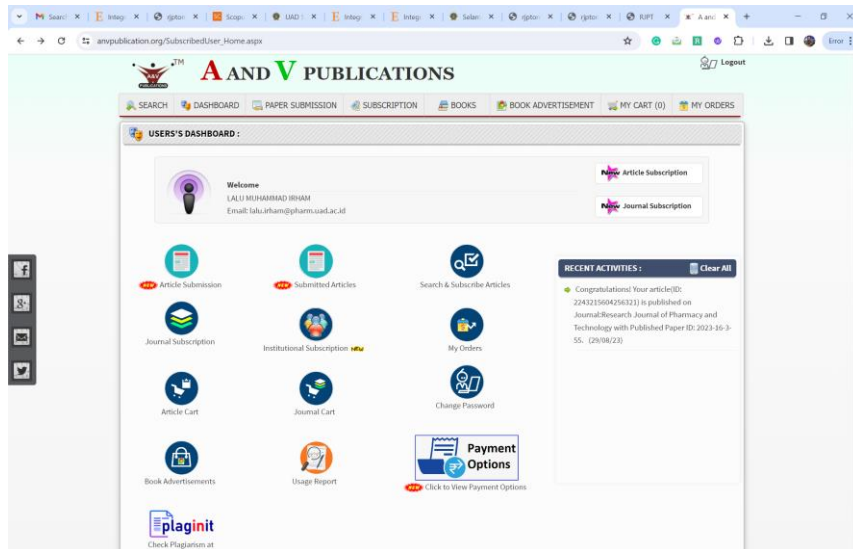
AUTHORS' CONTRIBUTIONS:
LMI and ZN conceived and designed the study. LMI and ZN performed all data analyses. LMI, ZN, DAP, YRN, WA, HD, RM, MAS and RC interpreted the results and revised the paper. LMI wrote the manuscript. All authors read and approved the final manuscript.

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