Trends in drug repurposing for chronic hepatitis-B infection: bibliometric-based approach 1990-2024

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Abstract. Chronic hepatitis B (CHB) infection is still a world problem today, especially in the developing countries. Until now, treatment related to CHB is still being continuously pursued using a variety of the latest approaches. One of today's scientific efforts that can accelerate drug discovery for CHB is by using the concept of drug repurposing or drug repositioning. Our research drug trends using a drug repurposing approach for CHB from 1990-2024. To find the related data, we used some words include “drug repurposing, drug repositioning, drug retasking, drug re-profiling, drug recycling, drug redirection and therapeutic switching”. The study trends we analysed were from 1990-2024, with details of 259 documents originating from 189 journals. The types of articles nominated included 134 original articles and 105 documents review articles. The most dominant drug repurposing study trend in 2021 (46 documents), subsequently followed by 2022 (39 documents), 2020 (33 documents) and 2023 (24 documents). The countries with the highest level of paper citations related drug repurposing are the USA and Germany. our findings show a trend in studies related to the reuse of drugs for CHB in the latest of current decade showing serious focus given by scientists who are concerned about Hepatitis B

1 Introduction

Chronic hepatitis B (CHB) is a public health problem that has not been fully resolved in almost all the world. The problem of CHB infection still has an impact on around 249 million

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people worldwide [1]. Approximately 600.000 infected patients die each year due to HBV-related diseases, especially those that progress to hepatocellular carcinoma (HCC) [2]. CHB infection, if not treated quickly and appropriately, will cause cirrhosis and is reportedly still the main cause of HCC in many developing countries [3]. It is estimated that around 5% - 15% of the population are chronic carriers of hepatitis B in developing countries, whereas in North America and Western Europe only 1% of the population is chronically infected [4]. Meanwhile, HCC appears to be more common in Africa and Asia than in other parts of the world due to Hepatitis B infection [2]. Even though scientists have found a vaccine to prevent HBV infection, it is unfortunate that this incident is still frequently reported [5]. In Indonesia, for example, it is estimated that 4-20.3% of the healthy population suffers from hepatitis B. This infection is more common in developing countries. Approximately 90% of newborn HBV-infected babies will develop chronic infection [6].

The hepatitis B virus (HBV) infects more than 300 million people worldwide and is thought to be a common cause of liver disease and liver cancer. HBV is part of the Hepadnaviridae. HBV replicates via RNA and can infect the host genome [7]. HBV infection will progress quickly to acute and finally progressed into chronic hepatitis, as well as the development of liver cirrhosis and HCC if it is not monitored and treated properly [8]. Currently, two groups of antiviral drugs are available therapies for CHB. These two classes of drugs include (alpha interferon (IFN-α) and nucleos(t)ide analogues) [9]. Unfortunately, drug resistance of currently available CHB drugs is still a major problem in the treatment of CHB. Besides, another challenge in CHB therapy is due to the fact that CHB therapy cannot directly target viral covalently closed circular DNA (cccDNA) as a source of CHB antigen [10]. Despite substantial research, there are currently no specific drugs that can stop the progression of CHB[11]. Therefore, scientists are still working hard to find solutions with various approaches related to the challenges of CHB treatment including drug repurposing based approach and find the genes related CHB.[12]

Developing a new drug is estimated to take 15 years with funding of more than $1 billion from the drug discovery to drug development phase[13]. Unfortunately, reports from the United States Food Drug Administration (US FDA) ultimately approve less than 5% of new molecules that enter phase I clinical trials [14]. Most drugs fail in Phase II clinical trials, and at least 50% of these are due to lack of efficacy, while 25% are due to toxicity (Irham et al., 2022). Due to the lack of CHB drugs that can be used clinically with high effectiveness and are more precise, a new approach that has emerged to identify new drug targets is drug repurposing, also known as drug repositioning. This concept is an alternative approach to finding new indications for existing drugs or drugs in clinical trials[15]. There is a very potential prospect for utilizing old drugs to be used for new indications, especially for diseases where drug choices are limited or treatment costs are expensive (Irham et al., 2022). Drug repositioning is very important in drug development, especially in the drug discovery phase because it can reduce the costs of the drug discovery process significantly. In addition, drug repositioning can reduce the risk of side effects from the drug because the safety of repositioned drugs has previously been proven in humans and other preclinical animals. Additionally, because methods for safety evaluation and formulation development already exist, this strategy has a much shorter development timeline [15]. The reuse of sildenafil citrate for erectile dysfunction is the most successful example of drug reuse [16]. The reuse of sildenafil citrate for erectile dysfunction is the most successful example of drug reuse When Pfizer repurposed Sildenafil for the treatment of erectile dysfunction under the name Viagra, it became the market leader in the category with a market share of 47% in 2012, with global sales of $2.05 billion. Therefore, under these circumstances, drug repurposing is an alternative and promising strategy to accelerate the discovery of new drugs not only for common disease but also for CHB. With the aforementioned related to the problems that have occurred in the discovery and development of CHB drugs so far, bibliometrics analysis has

been utilized to analyse the trends of drug repurposing for CHB. Bibliometric analysis is one of the most widely used methods for assessing the credibility, quality and impact of a scientific work. One of the efforts for this analysis is to relate the frequency of citations to the number of articles cited by researchers. Therefore, scientific work will benefit from the most frequently cited articles[17]. The impact of an article over time as demonstrated by the number of articles cited is measured by citation data. In addition, bibliometrics serves as a tool for discovering understudied research topics within a particular disciplinary field. This generates new research ideas[18].

Bibliometric analysis related to studies on chronic Hepatitis B was carried out to determine whether the research was interesting to conduct and to analyze the extent to which studies trended regarding the drug repurposing approach for CHB annually. Information about CHB disease research is presented in the bibliographic data. This study will help map publication data in the form of visualization data that is easier to understand in order to obtain useful information, such as keywords to determine research themes in certain scientific disciplines, author affiliations with certain journals to determine the geographical coverage of journals, and institutional collaboration. Bibliometric mapping is very important ; helping both the scientific community and the general public. The aim of current study to provide an overview of drug repurposing CHB disease research trends throughout the world. Infections are one of the focuses of the Sustainable Development Goals (SDGs) in the key field of communicable diseases, making this paper a potential solution.

2 Material and Methods

This research uses bibliometric analysis which includes Document Type and Language, Publication Development, Most Used Keywords, Citation Analysis and Number of Articles Cited, Most Cited Countries related to study trends related to CHB and drug repurposing. Our study focused on the document with English language. Therefore, that all documents other than English will be excluded.

2.1 Database

Research related to drug repurposing for CHB utilizes data from Scopus which were published from 1990-2024 (scopus.com/search). SciVerse Scopus is one of the databases that can be accessed online to find publications relevant to this research (accessed on 04/27/2024). Scopus was used in this research because it has many prominent advantages compared to other online databases [19]. First, this database provides comprehensive and detailed information with a variety of features such as countries, authors, journals and institutions involved. Second, this database also provides a number of citation data for each group of documents per scientific category, which functions as a matrix for determining the reputation of researchers throughout the world. [20].

2.2 Bibliometric Indicator

The bibliometric analysis criteria used in research are as follows: (1) document type and language, (2) development of publications, (3) keywords that are more widely used by researchers, (4) citation analysis and the number of articles cited, (5) the ten most cited countries, (6) the top ten most active journals and (7) international collaborations. Data on active, productive and most cited publications is also collected directly from the Scopus database by counting the number of documents cited from each publication. In addition, data on publications with the most citations comes from the Scopus database by counting articles

and citations for each country each year. Two application programs used to visualize data include: VOSViewer version 1.6.16 [21]Biblioshiny [22].

3 Results and Discussion

This research aims to analyse publication trends related to the use of old drugs for new indications, known as drug repurposing. In this research, more specifically, we want to look at publication trends related to drug repurposing, especially in CHB disease throughout the world. This research utilizes documents that have been published in the Scopus database. The database collected from the Scopus website was analyzed using VOSViewer and Biblioshiny, obtaining main information regarding studies related to chronic Hepatitis B which presents information about study data in the time span from 1990 to 2024.

3.1 Document Type and Language

Our research utilizes articles related to drug repurposing in CHB with English language criteria that have been published in the Scopus database during the period from 1990 to 2024 (Table 1). Uniquely, we found 259 related studies related to drug repurposing in CHB, including articles in 134 documents with research article category, review of 105 documents and 20 documents in other forms. The majority of articles we find are in the form of research articles. It indicates that the urgency related to research into drug repurposing in CHB is still very relevant considering that specific, more precise drugs have not been found to date. Besides, the fundamental reason is also related to the availability of sources and types of references that can be used in research related to drug repurposing for CHB.

Table 1. Main Information related Trend Drug Repurposing for Chronic Hepatitis B Infection 1990-2024

Description	Results
Main Information About Data	
Timespan	1990-2024
Sources (Journals, Books, etc)	189
Documents	259
Annual Growth Rate %	6.68
Document Average Age	6,18
Average citations per doc	53.14
References	19705
Document Contents	
Keywords Plus (ID)	6510
Author's Keywords (DE)	782
AUTHORS	
Authors	1616
Authors of single-authored docs	22
Authors Collaboration	
Single-authored docs	22
Co-Authors per Doc	6.64
International co-authorships %	23.55
Document Types	
Article	134
Book chapter	3
Conference paper	2
Editorial	5
Letter	3

Note	3
Review	105
Short survey	4

3.2 Trend Publication

Our research analyses the trend of studies from year 1990 to year 2024. Figure 1 shows the trend of publications increasing annually. The trend of related study in 2021–2022 shows the highest number of publications compare to other year. However, for year 2024 remains incomplete the number of documents was retrieved due to the time of data obtained in the middle of year, within the data collection period of April 27 2024. The increasing publication trend shows that research related to CHB is still interesting to discuss today.

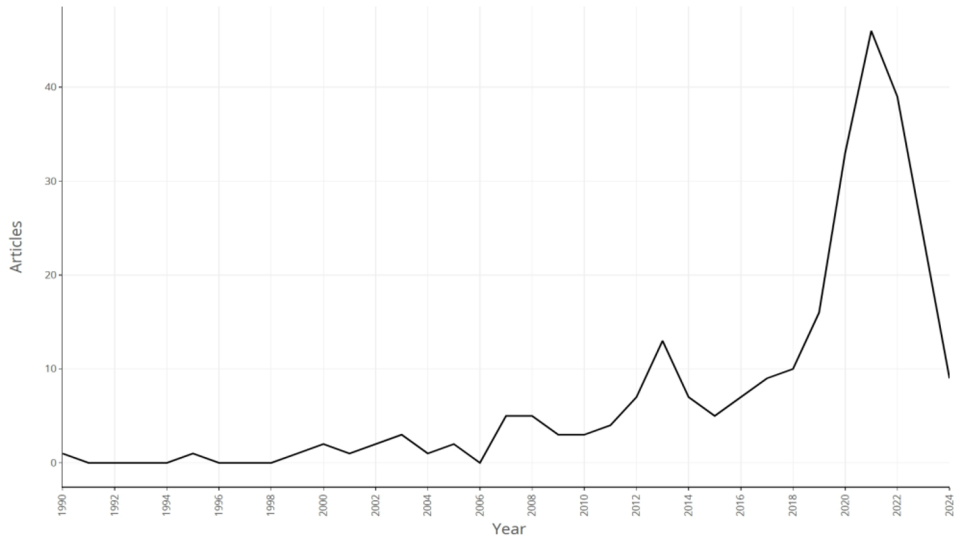

Fig 1. Annual Scientific Production Trend Drug Repurposing for Chronic Hepatitis B Infection 1990-2024

3.3 Most Used Keywords

The keywords most frequently used by authors include Chronic hepatitis B, hepatitis B, drug repurposing, drug repositoning, re-profiling, drug and recycling, drug and redirection, therapeutic and switching. The keyword drug repositioning also appears as a keyword used by the most authors. The following image shows the breadth of keywords used and their relationship to other keywords. The bibliometric mapping results from the VOSViewer application show that there is an increasing relationship between the two keywords (drug repurposing and drug repositioning), as in Figure 2 shows a correlation between drug repurposing and drug repositioning in drug discovery for CHB. The yellow colour indicates the newness of terms that tend to be frequently used in research related to drug repurposing in CHB. while the green and bluish lines indicate that the term was used earlier.

Fig 2. Visualization of the most frequent author keywords (minimum occurrences of 19 times) related to the Trend Drug Repurposing for Chronic Hepatitis B Infection 1990-2024

3.4 Citation Analysis and Number of Articles Cited

Table 2 and Figure 3 shows the top 10 most cited journal sources during the period 1990 to 2024. The trend of utilizing drug repurposing approach for various disease was identified such as for Covid-19 and inflammatory dissease. In the journal Nat Rev Drug Discov by author Li G regarding the study of drug repositioning entitled "Therapeutic options for the 2019 novel coronavirus (2019- nCoV)"[23] was cited the most 1242 times with an average of 248.40 citations per year. While for the second article with highest number of citation was [24]"Advances in the development of nucleoside and nucleotide analogues for cancer and viral diseases". However, based on the year of publication of the journal above, it shows that the latest journal is in 2021 with author Tschöpe C in the journal Cardiol with the title "Myocarditis and inflammatory cardiomyopathy current evidence and future directions" with a total of 556 citations with an average of 139 citations per year[25]. This will allow the journal to become a highly cited article in the future regarding research on Drug Repurposing for Chronic Hepatitis B Infection. In addition, this information will display journal sources that can help researchers choose the most appropriate journal to use in their research [26].

Table 2. Top 10 cited articles the Drug Repurposing for Chronic Hepatitis B Infection 1990-2024

Author	Year	Journals	PMID	Total Citations	Total Citation per Year
Li G	2020	Nature Reviews Drug Discovery	32127666	1242	248.40
Jordheim Lp	2013	Nature Reviews Drug Discovery	23722347	930	77.50
Thompson Ma	2012	JAMA	22820792	736	56.62
Tschöpe C	2021	Nature Reviews Cardiology	33046850	556	139.00
Günthard Hf	2016	JAMA	27404187	528	58.67
Seidah Ng	2014	Circulation Research	24625727	481	43.73
Kontermann Re	2011	Current Opinion in Biotechnology	21862310	448	32.00
Rossignol J-F	2014	Antiviral Research	25108173	397	36.09
Bonam Sr	2019	Nature Reviews Drug Discovery	31477883	375	62.50
Rolain J-M	2007	International Journal of Antimicrobial Agents	17629679	310	17.22

PMID : PubMed unique identifier

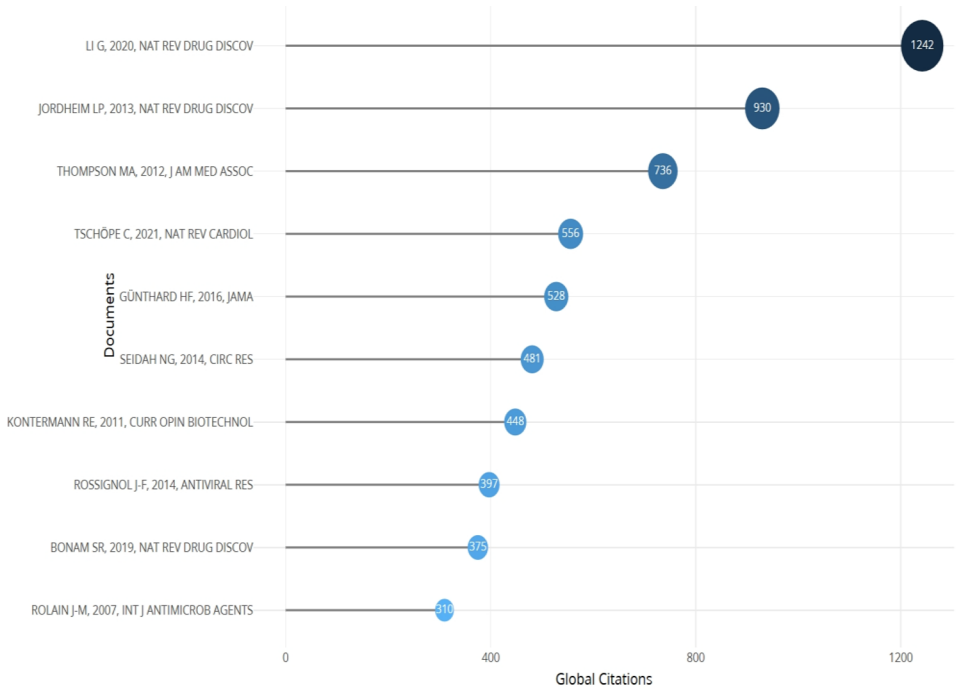

Fig 3. Top 10 cited documents related to the Trend of Drug Repurposing for Chronic Hepatitis B Infection 1990-2024

3.5 Most Cited Countries

Supplementary Figure 1 shows that the 10 most cited countries are dominated by the United States America (USA) and Europe. It can be concluded that the USA has 3702 citations which makes the country ranked first. Meanwhile, Asian countries are dominated by China with 911 citations and Singapore with 351 citations. This shows that there is still a lack of research related to Drug Repurposing studies on Chronic Hepatitis B Infection in Asia, especially in Indonesia and African countries. Of course, this information is anomalous information considering that the highest prevalence rate of CHB is in Asian areas, but not much research has been carried out by countries originating from Asian countries themselves. The hope for the future is of course that there will be more institutions in Indonesia that will carry out research related to diseases that focus on Drug Repurposing such as CHB.

3.6 Journals in publishing Drug Repurposing

In Supplementary Figure 2, there are 10 articles which show the number of documents published by various scientific journals in certain fields. The following are several important points based on antiviral research publication trends, this journal has a high number of publications with 11 documents, the journal of hepatology also has a significant number of publications with 6 documents, viruses, the number of publications here is lower than the previous two journals, drugs the number of publications in drugs is relatively low, Frontiers in immunology and frontiers in pharmacology both have a significant number of publications, Plos one, World journal of gastroenterology, and Computers in biology and medicine the number of publications in these three journals varies and drug discovery today. The number of publications here is also quite varied. This graph provides an overview of research trends in this field, with a focus on the journals that are most active in publishing scientific.

3.7 Collaboration among multiple continents

In the scientific field, cooperation between countries is very important. Scientists around the world can collaborate to share information related to a particular field with each other. According to Prieto et al.,2019 [27], collaboration between countries can help spread knowledge and provide access to funding for countries or organizations that cannot afford advanced technology. One Country Publication (SCP) is a type of article written by several authors from the same country and is an example of collaboration between countries. Meanwhile, Multi Country Publication (MCP), where all authors come from different countries and the publication represents collaboration between countries[26]. This MCP is very useful because it will be cited more often than the One Country Publication (SCP) [28]. The most author collaborations related to the Drug Repurposing for Chronic Hepatitis B Infection study for SCP are China, followed by the USA, India, Japan, Korea, Germany, where Indonesia and Belgium are the least. Meanwhile, the most author collaborations for MCP are the United States, China, Germany and China. where Japan and Korea have the least number of MCP researchers and even Pakistan has no researchers collaborating on MCP (**Supplementary Figure 3**).

Based on our findings, the USA is the country with the largest number of collaborating countries, followed by China and India which are ranked second and third respectively. Visualization of collaboration between countries with productivity with a minimum of 50 documents. Contributions and collaborations of authors from developed countries such as the United States and China still dominate in this study, followed by India, Germany and Japan. Authors from Indonesia still contribute little to research related to Drug Repurposing for

Chronic Hepatitis B Infection. This could be an opportunity for educational institutions in Indonesia to increase the production of scientific work with the aim of sharing knowledge, ideas and technology in order to compete with other countries in Southeast Asia [29]. Research on drug repurposing in the current decade has been widely utilized with various OMICS approaches [30]. We look forward to future Drug Repurposing studies for CHB Infections. As previous research develops, it shows that interest is increasing and it is interesting to research. Writers from developed countries such as America and China play the largest role in writing related articles. Even though Indonesia is a developing country with a high incidence of hepatitis B, Indonesia can collaborate with other countries (for example developed countries) to increase the production of scientific work to contribute to the development of medical science, especially in drug discovery and drug development for hepatitis B. CHB. Research on Drug Repurforming is still needed to advance Hepatitis treatment. Overall, strengthening collaboration, leveraging existing knowledge, and continuing research on drug repurposing will contribute significantly to the advancement of CHB treatment. Let's work together to improve health outcomes for those affected by these conditions.

4 Conclusion

The trend of publication of articles related to the Drug Repurposing for Chronic Hepatitis B Infection Study from 1990-2024 increases every year with the highest peak in 2021-2022. This research illustrates that research on drug repurposing for CHB disease is increasingly interesting and interesting to research. Most authors write articles from developed countries such as the US and China. Even though Indonesia is one of the countries with the lowest rate of ulcerative Hepatitis B cases, the country can work together with other countries to increase scientific research to help progress in the field of science, especially in terms of making Drug Repurposing-based drugs.

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Data will be made available on request.

Declaration of competing interest
The authors disclose no conflict.

Author contribution statement
L.M.I. and W.A. conceived and designed the study. L.M.I. and W.A. performed the computational analysis. L.M.I, D.P.A. wrote the manuscript. L.M.I. provided the funding. D.P.A., D.S. and R.C., S.P., S.K., revised the manuscript. All authors have read and approved the manuscript and have made significant contributions to this study.

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