

YEAST IN BIOPHARMACEUTICAL SCIENCES: VISUALISATION OF RESEARCH LANDSCAPE AND A BIBLIOMETRIC ANALYSIS

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ABSTRACT

The current study aims to analyse the trend in yeast research within the domain of biopharmaceutical sciences. Bibliographic information of the 1,000 most cited publications on yeast research in biopharmaceutical science was retrieved from the Scopus database. The data was then analysed by using bibliometric approaches. The data indicated a steady increase in publication numbers. The United States, Japan and China were among the highest research output countries. A total of 25 top core journals were identified. The keywords with the highest frequency included production, study and activity. To conclude, the current bibliometric analysis provides information that may be useful in locating research hot spots and gaps in the research area of yeast in biopharmaceutical science.

Keywords: Yeast, Bibliometric, Scientometric, *Saccharomyces cerevisiae*, VOSviewer

INTRODUCTION

Biopharmaceuticals are therapeutic substances from biological origins. Also called biologics, they are manufactured in living organisms such as bacteria, yeast and mammalian cells (Rader 2008). Biopharmaceutics, on the other hand, is defined as the study of the chemical and physical properties of drugs and it mainly involves drug absorption process (Panchagnula and Thomas 2000).

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Yeast is a unicellular organism that shares the characteristics of eukaryotes where the fundamental cellular mechanisms of replication, cell division, recombination and metabolism are highly conserved between yeast and higher eukaryotes, including mammals (Kim, Yoo and Kang 2015; Laukens, De Visscher and Callewaert 2015). One of the most highlighted advantages of yeast is that the culture of yeast can be done easily and it has a fast growth rate with a propagation time comparable to that of bacterial cells (Feldmann 2012; Huang, Bao and Nielsen 2014). Thus, the high productivity of yeast cells is effective in large-scale production of biopharmaceutical products (Botstein and Fink 2011).

Yeast is beneficial as a cell factory for the pharmaceutical production of insulin, human serum albumin and vaccines (Nielsen 2013). *Saccharomyces cerevisiae* is considered the best understood organism as it is the first eukaryotic organism to have its whole genome completely sequenced (Goffeau *et al.* 1996). Therefore, genetic modifications can be done easily as the immense amount of information is readily available (Huang, Bao and Nielsen 2014). Furthermore, yeast contains cellular organelles, that allow the production and folding of human proteins to be done correctly, including post-translational modifications. In addition, yeast is recognised as an ideal host for foreign protein secretion because it can produce high levels of protein and lower costs for downstream purification (Macreadie 2007). With the advancement of synthetic biology, *S. cerevisiae* has been genetically reprogrammed to produce and secrete the antibiotic penicillin (Awan *et al.* 2017). In the past decades, alternative hosts for biopharmaceutical production have been established from unconventional yeast species such as *Hansenula polymorpha*, *Pichia pastoris*, *Yarrowia lipolytica*, *Kluyveromyces marxianus*, *Kluyveromyces lactis* and *Scheffersomyces stipitis* (Kim, Yoo and Kang 2015; Lobs, Schwartz and Wheeldon 2017).

Bibliometric analysis is defined as 'the application of mathematics and statistical methods to books and other media of communication' (Pritchard 1969). In the past five decades, scientific publication has grown rapidly and become increasingly specialised. This has enhanced the difficulty in the evaluation of scientific research (Belter 2015; Alberts *et al.* 2014). Fortunately, bibliometric methods can be used to facilitate the assessment and appraisal of scholarly publications (Belter 2015). VOSviewer is an example of a bibliometric tool that employs the new mapping technique called visualisation of similarities (VOS) (Van Eck *et al.* 2010). VOS enables data mining and is capable of producing a large complex map from a large amount of data. In addition, VOSviewer was designed to make constructing and visualising bibliometric networks easy and it is available freely.

To the best of our knowledge, there is no bibliometric study so far to present the knowledge structure and development of yeast research in biopharmaceutical sciences, in a global setting. Therefore, in this study, we aimed to analyse and present an overview of the research trend in yeast research of biopharmaceutical science by a bibliometric method. The specific research questions that were addressed in the study are as follows: (1) What are the publications trends on yeast research in biopharmaceutical science from 1961 to 2019 in terms of influential countries, international collaboration, and productive journals? and (2) What are the specific research areas in yeast research of biopharmaceutical science that emerge from the data?

METHODS

Data Collection

Scopus is a multidisciplinary subscription database created and hosted by Elsevier. The Scopus database was selected to extract bibliometric data as previously reported by Chan *et al.* (2020). The data collected included publication details and citations of the 1,000 most-cited papers on yeast research for biopharmaceutical science. The data was extracted by searching the Scopus database with the following string: TITLE-ABS-KEY (Yeast) AND (Biopharmaceutical) OR (Pharmaceutical). The string searched for all the publications that contain any of these terms in their title, abstract or keywords.

Bibliometrical Analysis

The obtained data were analysed with regards to the publication year, publishing country, international collaboration and terms frequency (Chan *et al.* 2020). Bradford's law of scattering was applied only on the most-cited papers (excluding books and chapters) to identify the core journals as previously described by Yeung, Goto and Leung (2018). Keyword co-occurrence analysis was performed based on the terms extracted from the title and abstract of the 1,000 most-cited publications by adopting binary counting (Lozano, Calzada-Infante and Adenso-Díaz 2019). Additionally, VOSviewer was used to visualise the co-authorship analysis based on the countries with the aid of visualisation map (Van Eck and Waltman 2007).

RESULTS AND DISCUSSION

A total of 2,489 publications were found in the Scopus database from 1939 to May 2019. Among the 2,489 publications, the 1,000 most-cited ones were published during 1961 to 2019 (Figure 1A). A sharp growth trend was observed in 2001 to 2015, especially from 2011 to 2015.

We selected Scopus because Scopus has more journal coverage compared to Web of Science (WoS) and PubMed (Gorraiz and Schloegl 2008; Boshoff and Akanmu 2017). It is also noteworthy that Scopus included 1.04 times more articles than WoS (Vieira and Gomes 2009). Bartol and Mackiewicz-Talarczyk (2015) also reported that about two-thirds of the documents referenced in WoS and Scopus may be found in both databases. Therefore, it would create 'redundancy' when combining both online databases for a bibliometrical analysis. Google Scholar, on the other hand, when interrogated in this study, resulted in the highest number of documents. Google Scholar, given its free-of-charge nature, was shown to be practicing the 'quantity/breadth principle' and this could potentially serve as a weakness for bibliometrical purposes. Aguillo (2012) argued that the larger coverage of Google Scholar has been overrepresented by popular scientific literature, unpublished reports, and even teaching materials that make it 'lacks the quality control needed for its use as a bibliometric tool'. Finally, PubMed, is reported to have 'a smaller number of documents due to its narrower scope and coverage' (Alryalat, Malkawi and Momani 2019).

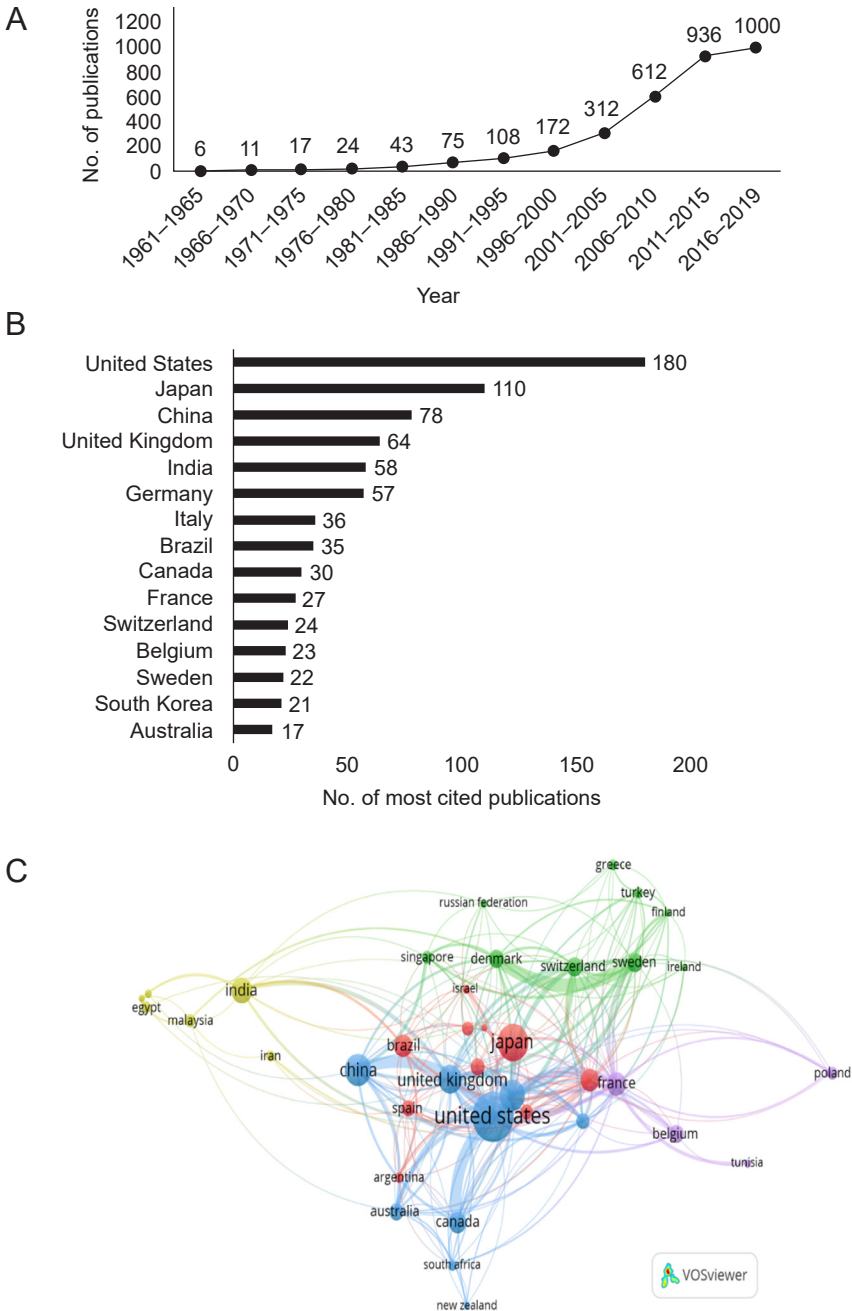


Figure 1: The trend of publications on yeast research in biopharmaceutical science. (A) The accumulated publications of the 1,000 top-cited publications across the year 1961 to year 2019; (B) The top 15 countries publishing the 1,000 most-cited papers; (C) The co-authorship analysis according to countries.

Next, to assess the role of geographical distribution, VOS analysis was performed based on countries and/or regions. The 15 most productive countries included eight European countries, four Asian countries, the United States, Brazil and Australia (Figure 1B). The leading country is the United States, which comprised 18% ($n = 180$) of the total publications, followed by Japan ($n = 110$, 11%), China ($n = 78$, 7.8%), United Kingdom ($n = 64$, 6.4%), and India ($n = 58$, 5.8%). With the goal to reflect the degree of collaboration between countries as well as the influential countries in this field, country co-authorship analysis was performed using VOSviewer. As shown in Figure 1C, the bigger nodes represent the influential countries with a higher number of publications. The links between the nodes represent the cooperative relationship among the countries. The distances between the nodes and the thickness of links indicate the level of cooperation among countries. It can be observed that most of the international collaborations were between the developed countries.

Based on Bradford's law of scattering analysis, the top cited papers were published in a total of 464 journals. However, only the top 25 core and active journals are shown in Table 1. The most prolific journal in this field was found to be the *Chemical and Pharmaceutical Bulletin* which published the highest number of papers ($n = 51$, 5.2%) on yeast research in biopharmaceutical sciences, followed by the *Applied Microbiology and Biotechnology*, and the *Biological and Pharmaceutical Bulletin*. As shown in Table 1, the impact factors (IF) of these 25 core journals range from 1.258 to 9.504. The *Proceedings of the National Academy of Sciences of United States of America* has the highest impact factor (IF = 9.504), followed by the *Current Opinion in Biotechnology* (IF = 8.380) and the *Metabolic Engineering* (IF = 7.674). Notably, the *Proceedings of the National Academy of Sciences of United States of America* also has the highest SCImago Journal Rank (SJR), Source Normalized Impact per Paper (SNIP) and CiteScore values (Table 1).

In this study, the *Chemical and Pharmaceutical Bulletin*, despite having a lower impact factor than the *Applied Microbiology and Biotechnology*, was shown to publish the highest number of papers on the investigated domain. This could be due to its more specific aims and scopes, ranging from chemical biology to pharmaceutical engineering. Meanwhile, the *Applied Microbiology and Biotechnology* has a wider scope which focuses not only on prokaryotic or eukaryotic cells, but also on genomics and proteomics; and more. Chan *et al.* (2020) studied the relationship between the impact factor and publication count regarding the research on culinary and medicinal mushrooms. The results clearly indicated that there was an insignificant negative correlation between the two variables. It is thus postulated that the decision of a choice of journal could be largely due to other factors besides the journal's performance.

Table 1: The list of top 25 core journals publishing the top cited papers on yeast in biopharmaceutical sciences

No	Source title	No. of papers	2017 impact factor ^a	5-year impact factor ^b	SJR ^c	SNIP ^d	CiteScore ^e
1	Chemical and Pharmaceutical Bulletin	51	1.258	1.242	0.364	0.566	1.29
2	Applied Microbiology and Biotechnology	40	3.340	3.602	1.182	1.161	3.64
3	Biological and Pharmaceutical Bulletin	40	1.694	1.766	0.626	0.674	1.71
4	Microbial Cell Factories	25	3.831	4.295	1.443	1.227	4.20
5	Process Biochemistry	13	2.616	2.987	0.761	1.012	2.77
6	Current Opinion in Biotechnology	12	8.380	8.180	3.202	2.205	8.45
7	Biotechnology and Bioengineering	11	3.952	4.206	1.372	1.186	4.07
8	PLOS ONE	11	2.766	3.352	1.164	1.111	3.01
9	Journal of Pharmacy and Pharmacology	10	2.309	2.555	0.657	0.821	2.32
10	Biotechnology Journal	10	3.507	3.499	1.125	0.910	3.12
11	Metabolic Engineering	10	7.674	7.418	3.337	1.787	7.95
12	FEMS Yeast Research	10	2.609	3.022	1.308	0.787	2.91
13	Journal of Biotechnology	9	2.533	2.843	0.929	0.860	2.67
14	Proceedings of the National Academy of Sciences of the United States of America	8	9.504	10.359	6.092	2.626	8.59
15	Biotechnology Letters	8	1.846	1.779	0.621	0.695	1.91
16	Science of the Total Environment	7	4.610	4.984	1.546	1.650	4.98
17	Journal of Biological Chemistry	7	4.010	4.253	2.672	1.085	4.04
18	Journal of Industrial Microbiology and Biotechnology	7	3.103	2.859	1.107	1.020	3.24
19	Industrial Crops and Products	7	3.849	4.072	1.091	1.668	4.19

(continued on next page)

Table 1: (continued)

No	Source title	No. of papers	2017 impact factor ^a	5-year impact factor ^b	SJR ^c	SNIP ^d	CiteScore ^e
20	Yeast	6	2.283	2.228	1.172	0.924	2.36
21	Environmental Science and Technology	6	6.653	7.250	2.535	1.941	6.58
22	Letters in Applied Microbiology	6	1.471	1.848	0.616	0.750	1.81
23	Advances in Biochemical Engineering/Biotechnology	6	2.795	2.464	0.788	1.431	2.37
24	Applied and Environmental Microbiology	6	3.633	4.272	1.684	1.224	3.99
25	World Journal of Microbiology and Biotechnology	6	2.100	2.031	0.604	0.810	2.14

Notes: ^a Impact factor based on the 2017 Journal Citation Reports® (Clarivate Analytics, 2018); ^b 5-year impact factor based on the 2017 Journal Citation Reports® (Clarivate Analytics, 2018); ^c SJR: SCImago Journal Rank based on year 2017; ^d SNIP: Source Normalized Impact per Paper; ^e CiteScore data from 2017.

A network map of the most frequently appeared terms was generated by the VOSviewer software to visualise the recurring terms (Figure 2). VOSviewer analysis shows that the percentage of yeast related publications in the field of biopharmaceutical has been soaring in recent years. A total of 47 terms met the threshold with a minimum number of occurrences at 50. As stipulated in Figure 2, the distance between the nodes refers to the strength of relation between two nodes. A closer distance between two nodes reveals a stronger relation between them. The thicker the line is, the greater the co-occurrence of terms.

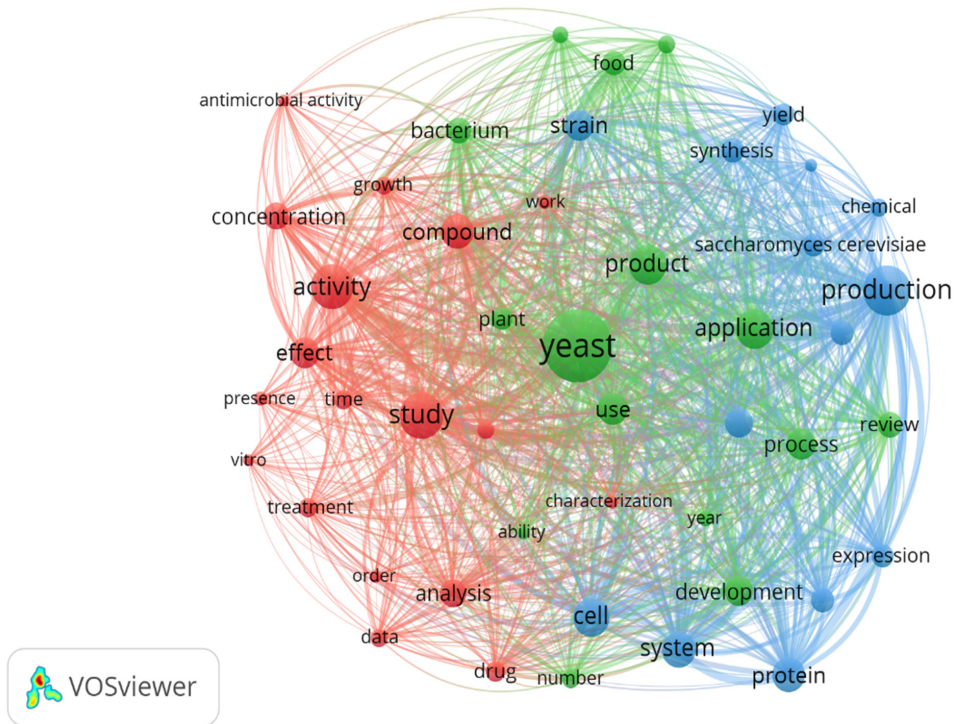


Figure 2: The co-occurrence network of the most frequently appearing terms in the title and abstract of the 1,000 top-cited publications.

It is noted that yeast, cell, strain, activity and effect are among the most repeated terms in 2006. Post 2006, the trend was more focused on application, production, pharmaceutical and processes (Table 2). The keyword co-occurrence analysis can effectively reflect the research hotspots in different fields, providing auxiliary support for scientific research (Cheng *et al.* 2018). From these terms, we found that the current attention on yeast research in pharmaceutical science mainly focuses on biochemistry, genetic and molecular biology, as well as in the subject area of pharmacology, toxicology, and pharmaceuticals. Indeed, yeast has been used as a system to study the antimicrobial, anti-inflammatory and estrogenic activity of some pharmaceutical ingredients and excipients as outlined by Korhola (2018).

Table 2: The top 20 terms that appeared the most in the title and abstract of the 1,000 top-cited publications.

Terms	Occurrences	Total link strength	Average published year
Yeast	594	4,442	2006
Production	370	3,161	2009
Study	337	2,693	2007
Activity	321	2,382	2007
Application	280	2,369	2008
Product	276	2,298	2007
Cell	263	2,117	2006
System	249	2,011	2007
Compound	235	1,881	2007
Protein	231	1,790	2008
Use	215	1,736	2005
Effect	206	1,631	2006
Strain	206	1,723	2007
Process	197	1,723	2008
Development	194	1,649	2008
Pharmaceutical	186	1,598	2009
Analysis	177	1,413	2008
Concentration	167	1,295	2006
Bacterium	163	1,451	2006
Review	158	1,318	2009

CONCLUSION

To conclude, this study can serve as an evidence-based reference for industries and researchers working with yeasts to identify the emerging research areas and hence facilitate the decision-making in drafting future research work. This study also provides insights to locate current research hotspots and gaps in yeast research. With this approach, scholars can appreciate the most cited content of the yeast research in biopharmaceutical science, as well provide evidence of the impact of research outputs when applying for research funding, finding new and emerging areas of research, and identifying potential research collaborators.

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