

Production of L-asparaginase: a bibliometric study

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ABSTRACT

During the last decade, L-Asparaginase has been used in the treatment of types of leukaemia. Many researchers have studied its molecular features, production, and application, resulting in more than 10000 studies published in the scientific base ISI Web of Science. Currently, this drug is not produced in Brazil, where heavy investments are made to import it. Facing this context, a group of Brazilian researchers proposed to develop the production steps of this biopharmaceutical. This work aims to contribute to the group by analysing the huge amount of information published in ISI through a bibliometric study and provide insights that can guide the group studies. Applying statistical and qualitative tools, it was possible to identify the main publisher journals and countries, the evolution of publications and themes, and the hot topics. This overview about L-asparaginase production can guide researchers to focus on areas that need more development.

1. INTRODUCTION

The enzyme L-asparaginase (L-ASNase) has been used as an anti-tumour treatment since 1978 (Batool *et al.*, 2016). Lymphomas are unable to produce L-asparagine, an essential amino acid for its growth, therefore, they depend on the reserves that are blood circulating, when L-ASNase is injected, it hydrolyses these reserves, causing tumour death by starvation (Verma *et al.*, 2007). Currently, the drug is not produced in Brazil, where heavy investments are made to import it (Menezes, 2016). L-ASNase has been studied for almost 90 years, therefore, there is a huge amount of publications about it. The aim of this work is to use bibliometry to provide insights to the research project managed by Prof. Adalberto Pessoa Jr. that objectives to develop the production steps of a new national biopharmaceutical of L-ASNase. Bibliometrics is a set of quantitative and statistical tools to analyse scientific communication, as journal papers, to measure the development of a research area (Thomson Reuters, 2008). Facing this context, this work purposes to provide an overview of the evolution of publications, main findings and themes and to identify

the principal journals and hot topics interesting to the scientific community to guide this research group in decision making to prioritize areas that need further development.

2. MATERIALS AND METHODS

2.1. Sampling

The sampling was performed in the scientific basis ISI Web of Science (webofknowledge.com) using the strings only “asparaginase” for the first search and “asparaginase” + “production or bioprocess” for the second. In addition, the papers were filtered by type “article” and “review”, since they are peer reviewed.

2.1. Data Analysis

The papers were analysed by the number of publications per year, journal, and country to understand the construction of this research area using the software Microsoft Excel. Following, the software VOSviewer (www.vosviewer.com) was used to design a co-occurrence network of the main keywords. To use it, first download the program and the file that contains the metadata of your research in ISI (Save to others format > Select the number of Records > Select the content > File Format: tab-delimited). Then upload this file in the software and choose the network to build. The third analysis was the hot topic identification according to the methodology proposed by Banks (2006). The terms were searched as “asparaginase” + “production or bioprocess” + term in ISI and the h-index was collected in the Citation Report. Subsequently, the m-index was calculated by dividing the h-index per total years. According to Banks (2006), terms with $m > 2$ are hot topics, $0.5 < m < 2$ are likely to be hot topics, and with $m < 0.5$ are of limited interest.

3. RESULTS

3.1 Panorama and Evolution

The first search about “asparaginase” resulted in 3423 papers and second specifically for “production or bioprocess”, in 274 articles and reviews. The journals that most published about asparaginase belongs to Medicine field of research, the main are Leukemia (77 papers), Blood (75) and Cancer (67). Approximately, 5% of the papers about bioprocess were published by Applied Biochemistry and Biotechnology (14). The countries with the highest number of papers were USA (986) for Asparaginase and, for bioprocess, India (88). Brazil ranked the fourth position in bioprocess with 14 papers. Figure 1 shows the evolution of published papers about asparaginase. L-ASNase has been studied since 1928 (Geddes and Hunter, 1928). The anti-lymphoma effect was discovered by Broome (1961), which leveraged the publications in the next decades. However, just

in the 90's with the breakthrough caused by PEGnologySM (Nucci et al. 1991), the publication rate enhanced again. Finally, the greatest innovation of 2000's was the gene expression studies that allow identifying genes linked to L-ASNase sensitivity (Scherf et al. 2000) and resistance (Holleman et al. 2004) associated with the treatment failure. Nowadays, the commercial drugs approved by FDA are Kidrolase or Elspar (native *E. coli* asparaginase), Erwinase (*Erwinia chrysanthemi* asparaginase) and Oncaspar (peg - *E. coli* asparaginase) (U.S. Food and Drug Administration, 2011).

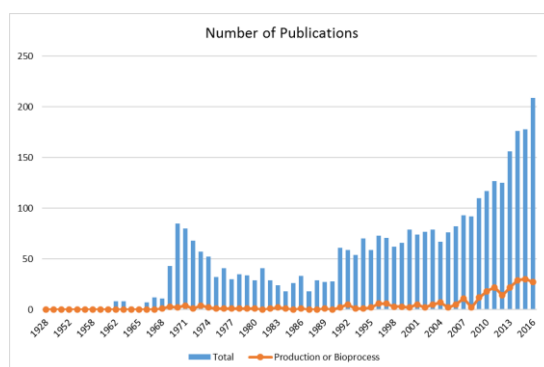


Figure 1. Evolution of the number of publications since 1928 to 2016.

3.2 Main themes

Through the analysis combined with "production or bioprocess", it was built the network of keywords with at least 10 occurrences, showed in Figure 2. Keywords are placed per the co-occurrence and the colours reveal the average year of publication. It is possible to conclude that bacteria still being the main used producer, especially *E. coli* (67 papers). Analysing the production step, studies focused first on cloning (15), after on fermentation (49), followed by purification (61) and expression (38). The tendencies point to the study of production parameters' optimization (33), reaction with acrylamide (29) and solid-state fermentation (8). The hot topic analysis is presented in Figure 3. According to Banks (2006), when associated "asparaginase" with "production or bioprocess" is likely to be a hot topic of a greater research area in the future ($m=0.7$). Furthermore, the topics purification, gene, substrate, and nitrogen source are also likely to be interesting to a greater community. Therefore, for new researchers, in the area, studies about Asparaginase + Production + Purification ($m=0.7$) are more interesting to the community than about fermentation ($m=0.3$). Otherwise, optimization ($m=0.4$) alone is not a hot topic, however, when adding fermentation + optimization the m -index increases to 0.6, pointing a probable hot topic.

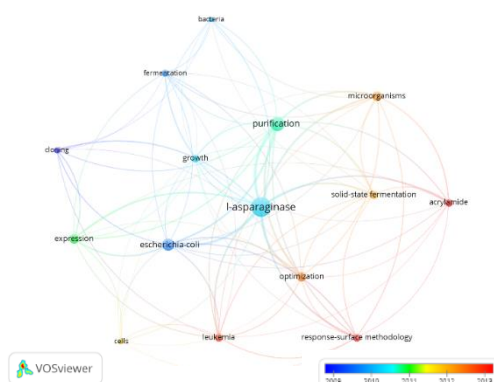


Figure 2. Network of main keywords about
 Production of Asparaginase.

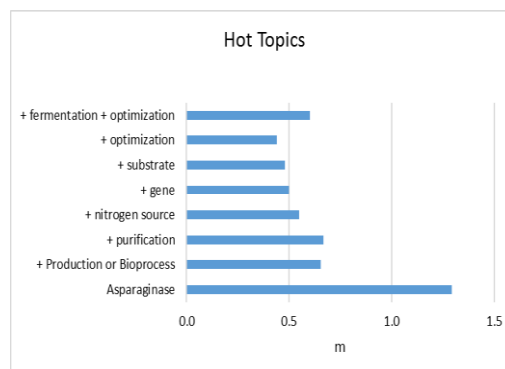


Figure 3. Probable hot topics interesting to the
 scientific community.

4. CONCLUSIONS

The results of bibliometric analysis can be explored by this research group to focus their studies on themes that are interesting to the scientific community aiming the increase of productivity. Furthermore, the techniques can be applied in any research area and help scientists to find interesting topics. Limitations are associated with the technique, Lameira et al. (2007) state that information can be lost, mainly, when analysing much data. Moreover, the result is subject to human biased analysis.

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