Production of the Scaffold Using 3D Bioprinting Applied to the Biomedical Area: A Bibliometric Study

Ana Paula Bispo Gonçalves[1*], Willams Teles Barbosa[2], Jaqueline Leite Vieira[1], Josiane Dantas Viana Barbosa[2], Milena Botelho Pereira Soares[1,2]

[1]Oswaldo Cruz Foundation, Fiocruz; [2]SENAI CIMATEC University Center; Salvador, Bahia, Brazil

Tissue Engineering is an ascent area with clinical applications through combining cells and biomaterials to reconstitute organs and tissues using scaffolds. These are defined as porous, temporary, biodegradable three-dimensional supports used to mimic the structure of the extracellular matrix and stimulate specific cellular responses at the molecular level. Among the existing technologies for producing scaffolds, 3D bioprinting stands out as one of the most promising technologies that enable layer-by-layer deposition with precise control of the spatial arrangement of functional components. One of the most used biomaterials for the fabrication of scaffolds for application in Tissue Engineering is poly(lactic acid), PLA, a biodegradable, biocompatible, and non-toxic polyester, whose main application is in the regeneration and replacement of bone tissue. In this way, the present article aims to obtain a comprehensive view of the current scenario of PLA scaffolds obtained by 3D bioprinting for biomedical applications through bibliometric analysis. The research was conducted in the Web of Science database between August 16 and 17, 2022. The following set of keywords was used: "scaffolds" AND "PLA" AND "3D printing" AND "biomedical applications" OR "biomedical application," resulting in 2,351 publications in the last five years. The VOSviewer software was used as a bibliometric analysis tool to visualize country networks and keywords on the topic studied. Based on the results, it was possible to observe that China, India, and the USA are the countries that published the most on the subject, and Chinese institutions and authors are also responsible for a considerable part of the publication of documents. There was also an increase in publications in the last five years, reinforcing the research interest that strengthens Tissue Engineering.

Keywords: Scaffolds. PLA. 3D Printing. Biomedical Applications.

Introduction

Research indicates that people's life expectancy has increased. However, this population aging represents a relevant problem for the health system, demanding treatments related to bone tissue [1]. Tissue Engineering has received considerable attention in this context, becoming increasingly important in leading tissue development research [2]. This area includes knowledge about Engineering, Biology, and Medicine and aims to develop biomaterials to replace or repair already injured tissues or organs from scaffolds. These three-dimensional structures provide mechanical support in which cells can be grown to regenerate or construct new tissue [2]. Scaffolds also allow the association of nutrients and metabolites to the extracellular ambiance [3].

Biocompatibility, biodegradation, adequate mechanical strength, uniformly interconnected pores, and the ability to mold into different shapes or dimensions are essential requirements for materials used to manufacture scaffolds [4].

Factors such as three-dimensional structure and the interconnection of pores allow the infiltration of blood vessels from adjacent tissues to the interior of the scaffold [4]. As scaffolds are produced from biodegradable polymers, removing the implant is unnecessary, as is often the case with metallic materials, as they are expected to degrade as new tissue forms [5]. Besides, the scaffolds must also have an adequate chemical surface that favors cell adhesion, proliferation, and differentiation. Poly (lactic acid) is among the biomaterials used to manufacture scaffolds. Poly(lactic acid), PLA, is a biodegradable, biocompatible polyester and can be obtained from renewable sources [6-10]. Due to

Received on 22 June 2023; revised 28 August 2023.
Address for correspondence: Ana Paula Bispo Gonçalves. Rua Waldemar Falcão, 121, Salvador, Bahia, Brazil. Zipcode: 440296-710 . E-mail: anapaulabisgon@gmail.com.

J Bioeng. Tech. Health 2023;6(3):244-251

its mentioned characteristics, combined with good processability and mechanical properties, PLA has a significant interest in biomedical applications [11]. In Tissue Engineering, one of its main applications is in the development of scaffolds for the regeneration and replacement of bone tissue used alone or in combination with other biomaterials, such as polyglycolic acid (PGA), polycaprolactone (PCL) [12–14].

When used as scaffolds, PLA offers interconnected porous structures and ease of construction in different shapes and structures similar to the natural extracellular matrix [15,16].

The degradation of PLA is from hydrolysis, in which it releases lactic acid monomers that are not toxic. These compounds are present in the human body and are removed by natural metabolic pathways [10].

Manufacturing techniques such as additive manufacturing have emerged as new tools for manufacturing 3D scaffolds. 3D bioprinting is a method that consists of layer-by-layer deposition with precise control of the spatial arrangement of functional components with well-defined and reproducible architectures, allowing the creation of an accurate 3D model of bone tissue for a given patient [10,17].

The great interest in the possibility of the reproduction of biological tissues and organs is still driven by the growing need for personalized medicine, enabling bioprinting to establish itself in biomedical research [17]. In this context, this article proposes a bibliometric analysis of the 3D bioprinting scenario of PLA scaffolds for biomedical applications to provide a view of the scientific scenario regarding the principal countries, institutions, periodic, authors, and keywords.

Materials and Methods

Research published in scientific journals indicates that a particular topic or area of knowledge has aroused interest in the scientific community.

The activities for measuring scientific knowledge have been carried out through bibliometric techniques [18]. Bibliometrics corresponds to an information science research area whose main objective is to measure scientific production, encompassing quantitative methods adopted to analyze the most differentiated means of scientific communication [18]. Bibliometrics is also responsible for the quantitative approach and analysis of bibliographic data, such as the year of publication, countries, journals, and authors [18].

Data collection was carried out on the Web of Science platform, which corresponds to a database used enough for bibliometric analysis, as it includes extensive coverage of indexing of journals in several areas of knowledge [19]. The search was carried out on August 16 and 17, 2022. The set of keywords was used: "scaffolds" AND "PLA" AND "3D printing" AND "biomedical applications" OR "biomedical application," resulting in 2,351 publications. This research was made considering the publication date of the last five years. The data collected from each search were exported as "files delimited by tabs", including the complete record and cited references. The VOSviewer software (version 1.6.17, Leiden University, Leiden, Netherlands) was used in this work to construct and visualize bibliometric networks, enabling the extraction of information from publications and obtaining network maps related to the keywords.

The evaluation of documents obtained from the database search was divided into three phases (Figure 1). Phase 1 refers to data collection in the Web of Science, phase 2 corresponds to data visualization from documents exported to the VOSviewer software for bibliometric analysis, and phase 3 evaluates data to identify the main topics discussed in the research.

For the present study, information regarding the productivity of articles per year, countries, institutions, authors, and keywords of the subject studied will be evaluated. Table 1 summarizes the type of element analyzed and its objective.

Results and Discussion

Based on the graph of the number of publications per year (Figure 2), it is possible to observe an

Figure 1. Phases, main steps, and analyzed criteria applied in this study.

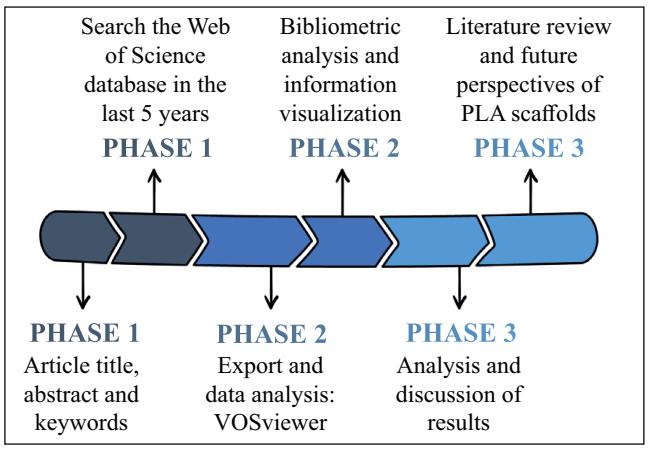


Table 1. Data evaluated in the study.

Analyzed element	Goal
Articles per year	Evaluate productivity through time
Countries	Identify the most productive and cited countries
Institutions	Identify the most productive institutions
Periodicals	Identify the most essential periodicals
Authors	Identify the authors who published the most on the topic
Keywords	Identify the most used keywords

increase in this factor in the last five years. This fact is due to the rise in research in Tissue Engineering.

Given the increase in the average life expectancy of people, the wear of tissues over the years, and trauma caused by impacts or diseases that cause tissue damage, it is necessary to use technologies to develop implant scaffolds [10].

From this perspective, scaffolds have recently received considerable attention in the scientific environment.

In 2022, the trend is for the number of publications to exceed previous years, as observed in 2018 and 2019.

The present study identified 2,711 institutions (affiliations) that published publications on the subject studied. The top ten institutions with the most published documents on PLA scaffold obtained by 3D bioprinting for biomedical applications are organized hierarchically in the TreeMap in Figure 3. Size and color represent numerical dimensions separated by institutions. The three institutions that published the most in the last five years were the Chinese Academy of Sciences, with 132 documents (5.6%); the Chinese Academic University of Sciences, with 43 documents (1.8%) and the Indian Institute of Systems, totaling 43 publications (1.8%).

Figure 4 shows the TreeMap of the top 10 periodicals that most published documents in the last 5 years with PLA scaffolds obtained by 3D bioprinting for biomedical applications. Among the three most cited periodicals are Materials Science Multidisciplinary, with 558 publications, corresponding to 23.8% of the 125 periods; Chemistry Multidisciplinary, with 328 publications (14.0%); and Nanoscience Nanotechnology, with 327 publications (13.9%).

Table 2 summarizes the types of published documents. These have been divided into three main categories. Of the 2,351 papers published, 69.4% were references to articles, 20.6% referred to review articles, and 8.9% were related to conference articles. The first type of publication

Figure 2. Number of publications per year.

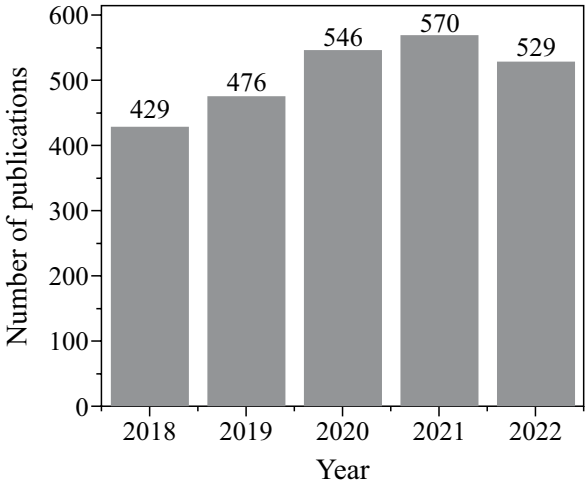
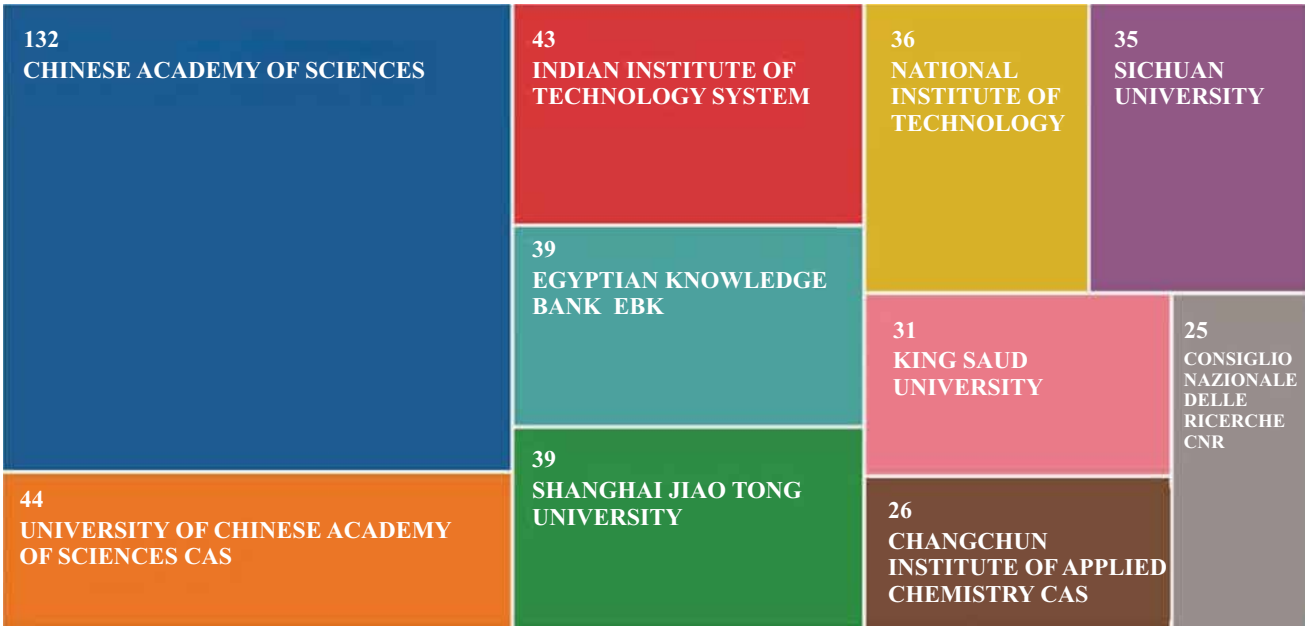
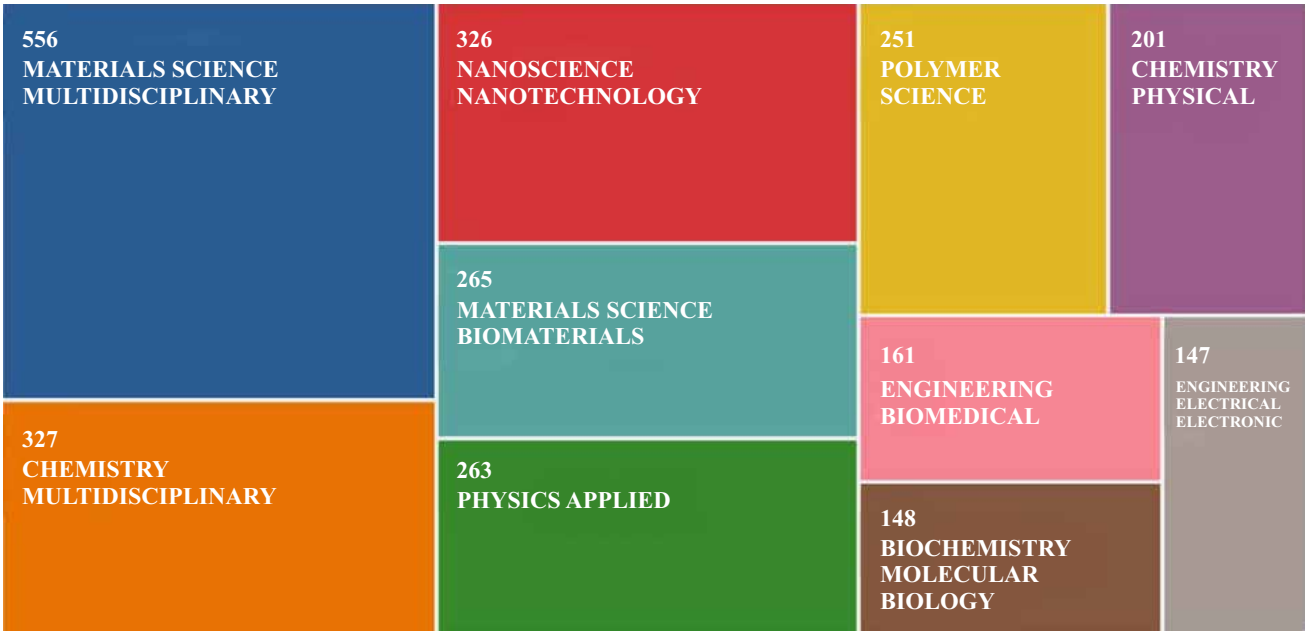


Figure 3. TreeMap is one of the top 10 institutions that published the most studies on scaffolds obtained by 3D bioprinting for biomedical applications.



Source: Web of Science (2022).

Figure 4. TreeMap is one of the top 10 periodicals with the most published papers on PLA scaffolds obtained by 3D bioprinting for biomedical applications.



Source: Web of Science (2022).

Table 2. Types of documents referring to the production of PLA scaffolds by 3D bioprinting for biomedical applications.

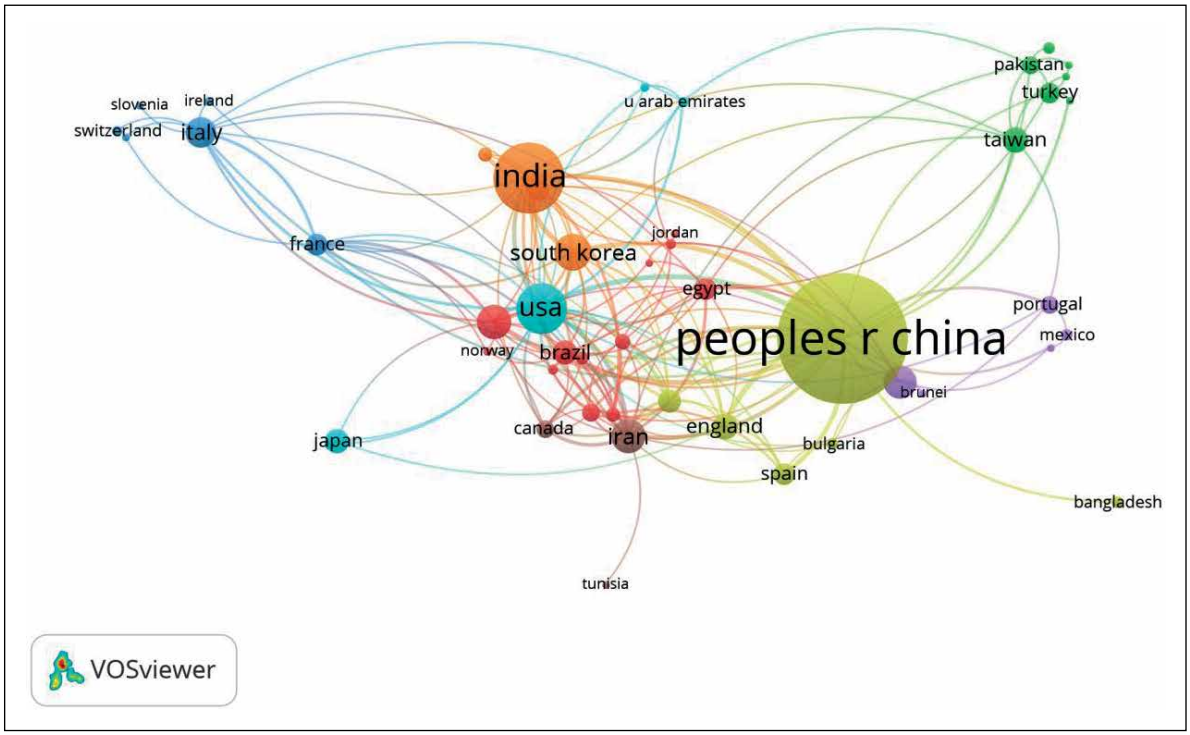
Type of documents	Number of documents published
Article	1,632
Review article	486
Conference article	211

reflects the study that addresses experimentally obtained results. On the other hand, review articles contemplate a general evolutionary perspective on the topic. On the other hand, conference articles are those presented at scientific events.

Figure 5 shows the countries that most published on the subject of 3D bioprinted PLA scaffolds for biomedical applications. It was observed that China (most emphasis in the Figure) is the country with the most published documents, with 520 publications, followed by India with 200 documents, and the USA with 117 publications. Brazil appears in the eighth position with 38 published documents. These data corroborate studies by Santoni and colleagues (2021) that point out the three countries mentioned among the most relevant in research involving 3D bioprinting [17]. In this work, the authors mentioned that although China occupies second place in leadership, just a few institutions have authors with many publications on 3D bioprinting [17].

The top ten authors with the most publications are affiliated with Chinese institutions (Table 3). These data corroborate with data from publications by countries, in which China appeared as the place where most published documents on that topic, and Chinese institutions were the ones that carried out the most studies on 3D bioprinting to obtain scaffolds for biomedical applications. It should be noted that many authors participate not only as

Figure 5. Network visualization of the most productive countries regarding scaffold research for biomedical applications by 3D bioprinting.



Source: VOSviewer (2022).

Table 3. Principal authors and many publications on producing PLA scaffolds by 3D bioprinting.

Authors	Number of publications	Percentage of the total number of publications (%)
Zhang Y	26	1,106
Wang Y	23	0.9878
Zhang L	21	0.893
Li J	17	0.723
Liu Y	17	0.723
Zhang H	17	0.723
Ramakrishna S	15	0.638
Wang L	15	0.638
Chen Y	14	0.595
Li Y	14	0.595

principal authors but also in studies in which they are co-authors contributing with partnerships with other institutions.

Figure 6 shows the connections between bibliometric data and the correlation between the scope of the study and the main research topics. It was necessary to evaluate each document and extract its main keywords. This analysis is relevant to determine ascent research, development, and innovation trends.

Repeated or irrelevant terms for this study were excluded. The distance between two or more circles is related to the strength of the connection between the terms represented by each one. In the image, different groups of terms are represented by different colors. The size of the circles is associated with the frequency of the appearance of the terms [20,21].

The number of clusters in each network map can change depending on the number of links. Considering the connections between keywords in each cluster, it was verified that the presence of four clusters was represented by different colors: yellow (cluster 1), blue (cluster 2), green (cluster 3), and red (cluster 4). In cluster 1, the most prominent term was "biocompatibility," with 83 occurrences and 524 connections. In cluster 2, "biomedical applications," "in-vitro," and "cells" are the most evident words. For cluster 3, "mechanical properties" was the most prominent term (81 occurrences) and was interconnected by 462 connections. The mechanical properties of the scaffolds, such as the tensile strength, should be as close as possible to the replaced tissue because if it is lower than that of the injured tissue, deformation of the implanted material may occur. Finally, in cluster 4, the most prominent term, "scaffold," is associated with applying the topic studied. One of the applications of tissue engineering is reconstructing cartilage and bone tissue cells, such as osteoblasts. So, the network map shows the connection between these keywords.

Conclusion

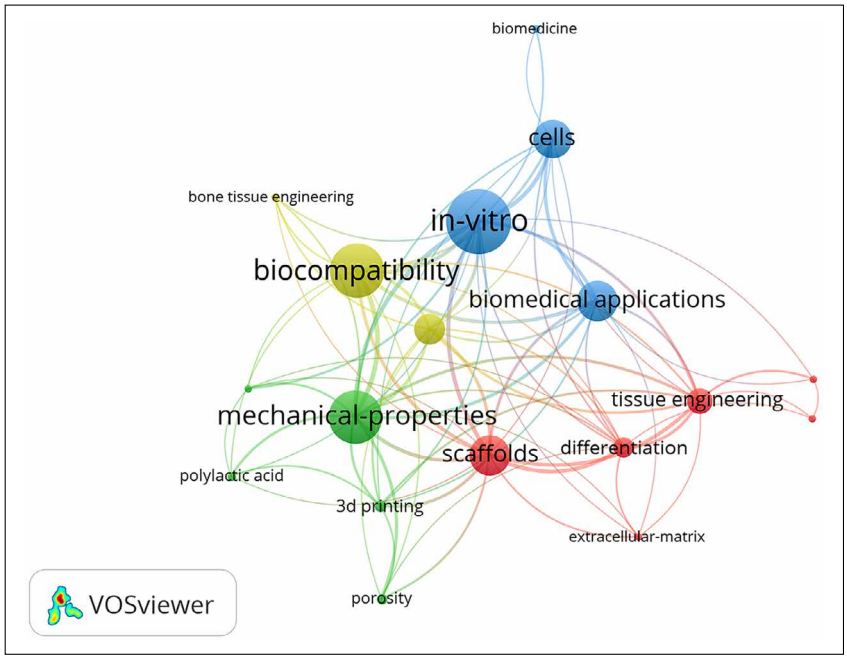
The present study showed an overview of the main topics related to scaffolds for biomedical applications that have been researched in the last five years. There was a trend in the growth of publications, which indicates that this topic has been attracting more and more interest.

Among the countries mentioned, China currently stands out as the country with the most publications on the subject studied, with 520 publications in the world, in addition to having the author with the highest number of publications, citations, and reference institutions for the publication of that country. The leading periodicals that publish studies on PLA scaffolds are multidisciplinary, confirming that Tissue Engineering encompasses several areas. From the analysis of the most cited keywords, it was identified that mechanical properties, biocompatibility, and biomedical applications are the main topics currently under study on scaffolds.

Acknowledgments

The authors thank Fiocruz and SENAI CIMATEC.

Figure 6. Network visualization of keywords based on total link strength.



Source: VOSviewer (2022).

References

1. Musalek C, Kirchengast S. Grip strength as an indicator of health-related quality of life in old age-A Pilot Study. Int J Environ Res Public Health 2017;14:1447. https://doi.org/10.3390/ijerph14121447.
2. Saji JJ, Malindisa ST, Ntwasa M. Two-dimensional (2D) and three-dimensional (3D) cell culturing in drug discovery. Cell Cult 2019: 1–23. https://doi.org/10.5772/intechopen.81552.
3. Williams DF. Challenges with the development of biomaterials for sustainable tissue engineering. Front Bioeng Biotechnol 2019;7:127. https://doi.org/10.3389/fbioe.2019.00127.
4. Geetha RB, Muthoosamy K, Manickam S, Hilal-Alnaqbi A. Graphene-based 3D scaffolds in tissue engineering: fabrication, applications, and future scope in liver tissue engineering. Int J Nanomedicine 2019;14:5753–5783. https://doi.org/10.2147/IJN.S192779.
5. Chocholata P, Kulda V, Babuska V. Fabrication of scaffolds for bone-tissue regeneration. Materials (Basel) 2019;:568. https://doi.org/10.3390/ma12040568.
6. Donate R, Monzón M, Alemán-Domínguez ME. Additive manufacturing of PLA-based scaffolds intended for bone regeneration and strategies to improve their biological properties, E-Polymers 2020;20:571–599. https://doi.org/doi:10.1515/epoly-2020-0046.
7. Balla E, Daniilidis V, Karlioti G, Kalamas T, Stefanidou M, Bikiaris ND., Vlachopoulos A, Koumentakou I, Bikiaris DN. Poly(lactic acid): A versatile biobased polymer for the future with multifunctional properties-from monomer synthesis, polymerization techniques and molecular weight increase to PLA applications. Polymers 2021;13(11).MDPI AG. https://doi.org/10.3390/polym131118228.
8. Gregor E, Filová M, Novák J, Kronek, Chlup H, BuzgoM, Blahnová V, Lukášová V, Bartoš M, Nečas A, Hošek J. Designing of PLA scaffolds for bone tissue replacement fabricated by ordinary commercial 3D printer. J Biol Eng 2017;11:31. https://doi.org/10.1186/s13036-017-0074-3.
9. Narayanan G, Vernekar VN, Kuyinu EL, Laurencin CT. Poly (lactic acid)-based biomaterials for orthopaedic regenerative engineering. Adv Drug Deliv Rev 2016;107:247–276. https://doi.org/https://doi.org/10.1016/j.addr.2016.04.015.
10. Serra T, Mateos-Timoneda MA, Planell JA, Navarro M. 3D printed PLA-based scaffolds, Organogenesis 2013;9:239–244. https://doi.org/10.4161/org.26048.
11. Sha L, Chen Z, Chen Z, Zhang A, Yang Z, Polylactic acid based nanocomposites: Promising safe and biodegradable materials in biomedical field. Int J Polym Sci 2016; 6869154. https://doi.org/10.1155/2016/6869154.
12. Grémare A, Guduric V, Bareille R, Heroguez V, Latour S, L'heureux N, Fricain JC, Catros S, Nihouannen DL,

Characterization of printed PLA scaffolds for bone tissue engineering. J Biomed Mater Res A 2018;106:887–894. https://doi.org/10.1002/jbm.a.36289.
13. Lopes TF, Levandowski A, da Fonseca SC, Zielak JC, Leão MP. Stem cells carrier scaffolds for tissue engineering, RSBO 2017;13:98–113. https://doi.org/10.21726/rsbo.v13i2.278.
14. Sartore L, Inverardi N, Pandini S, Bignotti F, Chiellini F. PLA/PCL-based foams as scaffolds for tissue engineering applications. Mater Today Proc 2019;7:410–417. https://doi.org/https://doi.org/10.1016/j.matpr.2018.11.103.
15. Bodnárová S, Gromošová S, Hudák R, Rosocha J, Živčák J, Plšíková J, Vojtko M, Tóth T, Harvanová D, Ižariková, G, Danišovič L. 3D printed polylactid acid based porous scaffold for bone tissue engineering: an *in vitro* study. Acta Bioeng Biomech 2019;21:101–110.
16. Tamaddon M, Blunn G, Liu C. 3D printed PLA/collagen hybrid scaffolds for bone-cartilage interface tissue engineering. Eur Cells Mater 2016;32:113.
17. Santoni S, Gugliandolo SG, Sponchioni M, Moscatelli D, Colosimo BM. 3D bioprinting: current status and trends—a guide to the literature and industrial practice, Bio-Design Manuf 2022;5:14–42. https://doi.org/10.1007/s42242-021-00165-0.
18. Costa M, Oliveira D. Ciência da informação e bibliometria: mapeamento da produção científica em periódicos brasileiros na temática educação a distância. Rev do Inst Ciências Humanas e da Informação Rio Gd 2020;34:19–44.
19. Guimarães A. Modelos de inovação: análise bibliométrica da produção científica. Brazilian J Inf Sci Res Trends 2021;15:e02106.
20. Van Eck NJ, Waltman L. VOSviewer Manual 1.6.11. Manual, (version 1.6.9), 2018.
21. Ji B, Zhao Y, Vymazal J, Mander Ü, Lust R, Tang C. Mapping the field of constructed wetland-microbial fuel cell: A review and bibliometric analysis. Chemosphere 2021;262:128366. https://doi.org/10.1016/j.chemosphere.2020.128366.