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Global Scientific Research Trend on Hydroxyapatite and Scaffold During the Period of 1991-2019: A Bibliometric Analysis

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In this study, a bibliometric analysis of hydroxyapatite (HA) and scaffold research using the online version of Science Citation Index (SCI) databases of the Thomson Reuters' Web of Science Core Collection from 1991 to 2019 was performed. The stages of the study included the analysis of the author's keywords, annual scientific production, and contributions of countries, institutions, and publication sources. Analysis of 8752 publications showed an increase in using HA-based scaffolds as a promising strategy to treat tissue defects. Global trend inclined toward the application of additive manufacturing (AM) to fabricate scaffolds. AM techniques such as Stereolithography, direct inkjet 3D printing, selective laser sintering, and fused deposition modeling seem to have more applications in production of ceramic-based scaffolds and will see further advancement in the coming years. Among 90 countries, the USA and China were countries that provided the highest number of publications during the investigated period. The most productive three institutions in this research area were located in China. Throughout the past 29 years, Journal of Biomedical Materials Research Part A, Materials Science, and Engineering: C, Journal of Materials Science: Materials in Medicine, Acta Biomaterialia and Biomaterials have the highest number of publications on HA and scaffold research.

Keywords: Hydroxyapatite; Scaffold; Bibliometrics.

1. Introduction

Bone is a highly organized natural ceramic composite that consists of the organic matrix (30%), inorganic nano-crystalline salts (60%) in the form of hydroxyapatite (HA), and water (10%) [1]. Collagen type I, triple helix with ~1.5 nm diameter and ~300 nm length, is a primary component (95%) of the organic matrix. HA crystals have a plate-like shape with a thickness of 1.5-4 nm and lengths of 50×25 nm [2-5]. Morphologically, bone is categorized into two forms: cortical (compact) and trabecular (spongy). Spongy bone is loosely arranged and has 50-90% porosity. However, densely packed cortical bone only contains 3-5% porous space for osteocytes and blood vessels. Osteons are considered as the building blocks of cortical bones, and their size is varying between 10-500 nm. However, a porous network of trabeculae forms the structure of trabecular bone [6-8].

The bone tissue experiences ongoing dynamic remodeling throughout life. This unique characteristic of bone is attributed to four different cell types, osteocytes, osteoblasts, osteoclasts, and bone lining cells, which gives the bone a potential to remodel itself and to sustain its healthy state or to restore the damage. However, in the recent years, an enormous require for bone substitutes or regeneration of bone tissue have been created due to increase in the number of bone tissue defects caused by trauma, diseases, and aging of the population [9-11]. Nearly 4 million operations using bone substitute materials and grafts have been reported annually [12,13].

In the last decades, tissue engineering and regenerative medicine have introduced as promising techniques for bone defect treatment[14,15]. In fact, a possible solution to overcome problems with traditional techniques is the generation of the engineered structure by a combination of scaffolds and living cells[16,17]. The main part of tissue engineering for bone is scaffold that serves as a structural template on which cells interact and form new tissue [18]. In other words, a scaffold is a 3D artificial structure that is used as support for new bone tissue formation.

Hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] is a potent bioceramic that resembles the inorganic part of human bone and tooth [19]. Hydroxyapatite (HA) has found numerous biomedical applications as bone tissue engineering scaffolds [9,20,21], bone fillers [3], bioactive implant coating [22,23], and drug or protein delivery systems [24-27]. The principal advantages of HAp are its wonderful biocompatibility, osteoconductivity, and bioactivity [28-30].

Scaffolds should have specific criteria in order to function properly, including mechanical properties same as bone, biocompatibility, appropriate biodegradability and porosity [31]. Scaffold with ideal design allows or even improves cell attachment, viability, proliferation, and osteogenic differentiation [32]. Fabrication method, structural features as well as biomaterial composition and biological requirements are four major modification that could be changed to achieve more successful bone tissue engineering. Porous 3D scaffolds, which have been synthesized by a variety of techniques and different materials, have been widely investigated in the literature [12,33,34]. The architecture of scaffold, including porosity, pore size as well as interconnectivity of pores is critical in bone tissue engineering. They are important for cell attachment, cell migration, cell-scaffold interaction, and mechanical properties

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of the scaffold [35-37].

Various fabrication routes could affect the architecture of produced bioceramic scaffolds. Each processing technique produces a different range of porosity, pore size, pore shape, pore distribution, and interconnectivity. These structural features determine the final performance of the scaffold to a considerably high degree by promoting cells attachment, proliferation, migration, as well as nutrient and oxygen diffusion [12,38]. Classical manufacturing refers to techniques such as solvent casting and particle leaching, thermally induced phase separation, freeze-drying, gas foaming, and powder forming [33,39]. On the other hand, additive manufacturing (AM) is any technique by which the object is fabricated layer by layer by the assistance of a CAD (computer-aided design) file. Stereolithography (SLA), fused deposition modeling (FDM), selective laser sintering (SLS), and inkjet 3D printing, are few methods [40]. Moreover, using nanofibers, generated by electrospinning, to fabricate scaffolds is another method that has been categorized separately in this study [41].

The limitations of conventional techniques opened doors to latter AM processes to manufacture scaffolds suitable for tissue engineering. The main advantage of AM methods over classical ones is their ability to almost precise control over structural features and obtain complex morphologies and accurate geometries [42,43]. As well, fabrication costs are reducing, due to a decrease in waste materials [44]. In the following, some of the most commonly used conventional and AM techniques used for manufacturing of ceramic-based scaffolds, as well as their advantages and disadvantages have been explained briefly.

Gas or direct foaming is one of the conventional methods to produce highly porous bioceramic scaffolds with wide pore size range between 20 μm to 2 mm [45]. Main problems of gas foaming method are low pore interconnectivity, no pore orientation, and poor control over pore size or even shape [46-48]. Solvent-casting and particle leaching is an alternative way to fabricate scaffolds, where salt particles leach out to achieve porous structure. The key advantage of this method is homogenous and at the same time controllable pore size, as well as high porosity. However, only low interconnected and simple shaped scaffolds could be generated using this process [49-51].

At the almost same way, some porous scaffolds were produced using polymeric particles that burnt out later in order to generate porosity. The space-holder method (organic phase burning-out) has advantages and disadvantages of salt leaching strategy [52,53]. Moreover, as a result of burning gases, cracks might be formed inside the structure, which should especially be considered in the fabrication of scaffolds with higher porosity [54]. Freeze-drying has been suggested by many researchers as another process to produce porous scaffolds [55]. Beside improved mechanical properties, controlled pore size/ distribution and even interconnectivity have been mentioned as benefits of freeze-drying route [56–58]. Weak points of freeze-drying such as long preparation time, formation of small pores with an irregular shape, existence of cytotoxic solvents, and high consumption of energy have been listed in literature [59,60]. Thermal induced phase separation was used as an alternative process to create microporous since 1978 [61]. By adding porogen and later leaching of it, the larger pore size can also be obtained, which result in better cell proliferation [62]. Achieving highly porous scaffolds with interconnected pores made this synthesis route appropriate for bone tissue engineering [63].

To overcome the shortcomings of scaffold-producing conventional routs, AM has been applied since the early 1990s and developed during recent years for medical applications [64-67]. Despite differences in techniques, all AM (3D printing) procedures are fabricating a final structure through adding layer of materials over the previous layer automatically. This process is accomplished by defining the desired structure using computer-aided design (CAD) file before layer-by-layer fabrication. Various material forms, such as powders, filaments, solidifiable fluids, and thin sheets could be used as primary materials in different 3D printing technologies [68].

Direct inkjet printing as the first 3D printer, developed in MIT, became popular due to its accuracy. Inzana et al. reported 20-50 μm range micropores in printed scaffolds [69]. This technique is based on dropping organic or water-based binder from the printer nozzle on powder layer to bind particles. Strong potential of direct inkjet 3D printing in the fabrication of geometrically well defined ceramic scaffolds for bone tissue engineering has been demonstrated in several studies [70-74]. However, this technique requires post-processing like heat treatment, considerable optimization, and high-priced instrumentation [64,75,76]. Also, some binders could be cytotoxic and should not be used in tissue regenerative applications.

Fused deposition modeling (FDM) uses thermo-plastic filaments, which are melted and extruded out of moving nozzle onto specific sites according to CAD file on layer by layer sequences. Although this technique is generally applied to fabricate polymeric scaffolds, there are studies that employed it to produce ceramic or composite scaffolds [77,78]. Resolution of scaffolds was one of the main issues to discuss when FDM would be used. Scaffolds with pore sizes larger than 200μm could be printed successfully [79]. Recently, combining FDM with other techniques, such as gas foaming, has allowed researchers to create scaffolds with customized macropores larger than 100 μm and micropores less than 10 μm [80].

Stereolithography (SLA) uses UV laser to crosslink polymer resin and built one layer at a time. Resin storage tank elevates up and the next layer is solidified again using light source selectively. Compared to other AM routes, SLA provides smaller structural features. Because UV beam-width is a factor that restricts minimum feature size (resolution) [66]. Laser beam-width of many commercially available SLA devices is limited to 250 μm [81]. Therefore, micro-SL technology has been employed to fabricate micro-sized features in tissue engineering applications. In a study, conducted by Wang and colleagues, the resolution of 50 μm has been achieved successfully [82]. Making ceramic-based scaffolds utilizing SLA has been investigated in many studies [83,84]. Sometimes, mixture of ceramic powder and photopolymers have been used as resin [85]. Moreover, indirect printing is another approach to fabricate ceramic structures by making SLA-imprinted negative replica [86]. Good control over pore size, shape, and interconnectivity to manufacture complex architecture of scaffold and high resolution are the most remarkable advantages of SLA technique [87]. However, finding appropriate biodegradable photocurable polymer is great challenge for SLA users [88]. Table 1 represents the summarized advantages and disadvantages of classical, additive manufacturing techniques, and electrospinning. In this study, a comparative bibliometric analysis was accomplished to detect the global tendency of HA used in scaffolds for bone tissue engineering from 1991-2019 for the first time. Manufacturing methods and materials used for the production of scaffolds, as well as the frequency of the publications using scaffolds, were analyzed in order to explore research patterns. Furthermore, research trends of scaffolds, especially hydroxyapatite base, in different periods and also different countries, institutions, and publication sources were inspected. Results of this study might play a role as a guide for future studies.

2. Methods

The methodology used in this bibliometric study was to trace publications using the online version of Science Citation Index databases of the Thomson Reuters' Web of Science Core Collection which collects thousands of publications each year and provides various useful records for each of them. "Hydroxyapatite" and "scaffold" were used as search phrases, and they were searched in

Table 1. Different scaffold manufacturing methods and their advantages and disadvantages [12, 18, 51, 64-67, 88].

Manufacturing method		Advantage	Disadvantage
Classical	Solvent casting/ particle leaching	• High regular porosity • Controllable pore size	• Poor mechanical properties • Low interconnectivity • Limited to simple shapes
	Gas foaming	• No chemical solvent • Low cost	• Difficult to control pore size and shape • Low interconnectivity • Difficult to the inclusion of cells and bioactive molecules to scaffold due to high pressure • No pore orientation
	Phase separation	• Capability to combine with other methods • Removing porogen leaching step • Highly porous and interconnected pores	• Using an organic solvent • Not able to produce large pore
	Freeze drying	• No need to solid porogen • Improved mechanical properties • Interconnected pores • No harms for environment	• Long processing time • Irregular porosity • High energy consumption • Cytotoxic solvents
Electrospinning		• Scaffold with a large surface area • Low cost and simple to use	• Scaffold with a large surface area • Limited mechanical properties
Additive manufacturing	Direct inkjet 3D printing	• Mild condition of process lets living cells and biomolecules plotting • Both ceramics and polymers • Well defined geometry	• Post-processing needed for some materials • Optimization • Cytotoxic binders • High-cost instrumentation
	SLA	• Complex internal architecture can be produced • Proteins and cell patterning is possible • High resolution	• Only photopolymers can be used • Finding biodegradable photopolymers
	SLS	• No support needed	• Resolution limitation because of laser width
	FDM	• No need for platform or support • Multiple nozzles for several materials	• Resolution limitation because of the nozzle tip • Limited materials because of the need for melted phase

terms of the topic within the publication year limitation from 1991 to 2019. Eight thousand seven hundred fifty-eight publications (8758) met the selection criteria. After the elimination of retracted publications, a total of eight thousand seven hundred fifty-two (8752) publications and their records were downloaded on 13 April 2019, and they were used for further analysis.

Downloaded records involved considerable information about the publications including title, abstract, year of publication, document types, names of authors, author affiliations, Web of Science categories of the publications, names of sources, and citations for each publication. Data were processed using spreadsheet software, and additional coding was performed manually. In order to estimate the contributions of different countries and institutions, author affiliations were analyzed. The term "single country publication" was assigned if addresses of all researchers' institutions were from a single country. For those publications that were co-authored by researchers whose institutions were not from a single country, the term "internationally collaborative publication" was assigned. The term "single institution publication" was assigned if all researchers were from the same institution. For those publications that were co-authored by researchers from more than one institution, the term "inter-institutionally collaborative publication" was assigned.

Contribution of institutions was calculated by assigning one point for each author of the publication from the corresponding institution. Similarly, the contribution of countries was calculated by assigning one point for each author of the publication from institutions that are located in the corresponding country. Publications that originated from England, Northern Ireland, Scotland and Wales, were reclassified and grouped under the heading of the United Kingdom (UK). In the same way, publications that originated from Hong Kong were reclassified and grouped under the heading of China.

Table 2. Document types and citation outputs.

Document type	TP	%	TC	CPP
Article	7465	5.96	1,049	2.01
Proceedings paper	522	5.96	1,049	2.01
Review	353	4.03	27,682	78.42
Article, Proceedings paper	304	3.47	9,394	30.90
Meeting abstract	760	0.87	48	0.63
Others	32	0.37	48	1.50
Total	8752	100.000	215,230	24.59

TP: total number of publications; TC: total number of times cited since the paper was published; CPP: citations per publication (TC/TP)

To a better tracing of the research trends during nearly the last three decades, the publication patterns were dissected into more comprehensive data, including manufacturing methods of scaffolds, and materials used to fabricate scaffold or accompanied with HA to make composite scaffolds. Note that the words that refer to the same concept have been accumulated under one phrase. For example, terms hydroxyapatite, HA, HAp, hydroxyapatites, apatite, and hydroxy apatite were accumulated under one keyword "hydroxyapatite."

3. Results and Discussion

Document types and their distribution at the Web of Science database have been analyzed for the research topic. Table 2 shows the document types and a total number of publications

(TP) for each document type as well as the outputs of citation analysis. TC represents the total number of times the publication has been cited since it was published. Moreover, citations per publication (CPP=TC/TP) is another important scientific result.

It is not surprising that the journal article is the most commonly used document type in the materials science field. A total of 7465 journal articles have been published since 1991, which correspond to 85.3% of the total publications. Journal articles are followed by proceeding papers with a total publication number of 522 and the corresponding percentage of 5.96%. Furthermore, document type of review has the highest CPP score of 78.42, which is followed by an article, proceedings paper (30.90) and journal article (23.71). Document types of proceeding papers, meetings abstract and others have relatively low CPP scores. In addition, it is necessary to indicate that the journal article is the most dominant document type in term of TP. However, when CPP is taken into consideration, it has the 3rd ranking.

For further analysis of the performance of publications, an annual number of articles during 1991-2019 was investigated. Firstly, the mean of total citations (TC) per publication was obtained for each year. In order to obtain a reasonable comparison of citation outputs, citable years were taken into consideration because it was not rational to compare the citation output of publications that were published in different years. Generally, there is a direct correlation between the frequency of citation and length of time interval since publication. In this regard, newly published articles are undervalued. For example, when citation output of two articles published in 1999 and 2017 are compared, the first one has 20 citable years although the latter one has only two years. If they were cited 120 and 60 times respectively, the performance of the first one seems to be superior to the other one. However, when citable years are taken into consideration the first article was cited six times per year, whereas; the latter one was cited 30 times per year. Thus, the latter has much better citation performance.

In Figure 1, annual number publications and mean total citations per publication per year (TC/TP/citable years) were displayed. It can be seen from the figure that in 2001 there is a peak in citation output (TC/TP/citable years). Cause of this peak is a research article having the title of "Self-Assembly and Mineralization of Peptide-Amphiphile Nanofibers" [89]. This article was published in "Science" journal, and it was cited 2,535 times. Thus, this article becomes an extreme outliner because only 19 publications were published in 2001. When the other 18 publications are considered without the extreme outliner, citation output drops down to 5.43 from 12.55, which is very close to the output of following years.

Moreover, it can be observed from the figure that scientific production in the research field is relatively low until 2001. However, after 2001 the topic becomes more popular, and scientific production rapidly increases. In the first ten years of research from 1991 to 2000, the average number of publications was 3.9 per year, whereas in the last decade average yearly production exceeded 700 publications.

Table 3 shows the top 25 most productive countries that have contribution to more than 90% of total scientific production on hydroxyapatite and scaffold research between 1991 and 2019. For better comparison country scientific production was examined in 3 time periods; 1991-2009, 2010-2014 and 2015-2019. Country scientific production was calculated by assigning one point for each author of the publication whose institution is located in the corresponding country. For example, for an article which is co authored by 3 authors whose institutions are not located in a

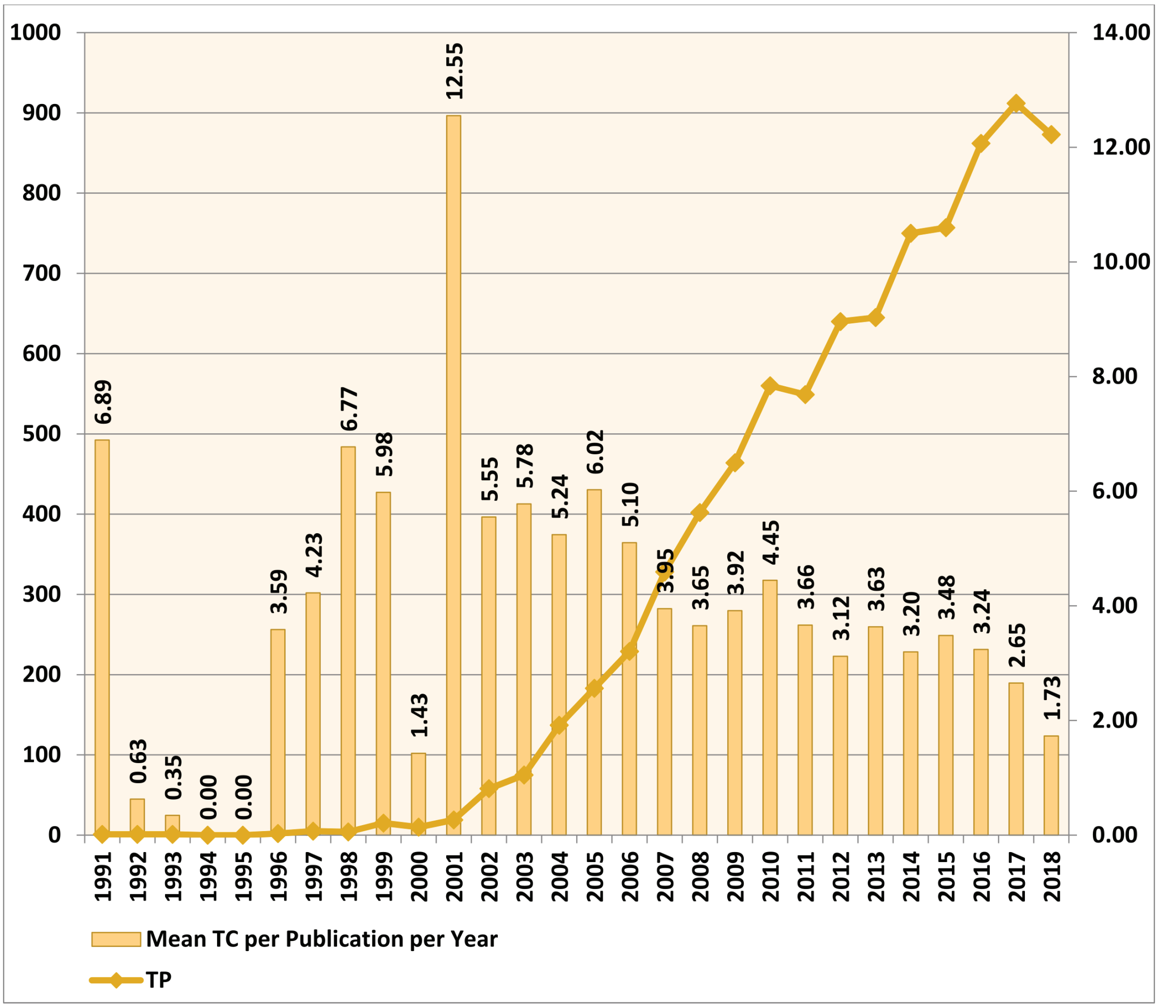

Figure 1. Annual number of publications and citations per publication per year.

Table 3. Country scientific production.

		1991-2019			1991-2009			2010-2014			2015-2019		
COUNTRY		FREQ.	RANK	%	FREQ.	RANK	%	FREQ.	RANK	%	FREQ.	RANK	%
CHINA		5381	1	21.44	749	□ 2	16.17	1867	▲ 1	21.04	2765	□ 1	23.85
USA		3176	2	12.65	812	□ 1	17.53	1220	▼ 2	13.75	1144	□ 2	9.87
SOUTH KOREA		1578	3	6.29	333	□ 5	7.19	668	▲ 3	7.53	577	▼ 5	4.98
ITALY		1465	4	5.84	249	□ 7	5.38	644	▲ 4	7.26	572	▼ 6	4.93
JAPAN		1314	5	5.24	483	□ 3	10.43	483	▼ 5	5.44	348	▼ 8	3.00
IRAN		1227	6	4.89	54	□ 17	1.17	353	▲ 7	3.98	820	▲ 3	7.07
GERMANY		1062	7	4.23	260	□ 6	5.61	385	□ 6	4.34	417	▼ 7	3.60
INDIA		973	8	3.88	79	□ 12	1.71	280	▲ 10	3.16	614	▲ 4	5.30
UK		964	9	3.84	359	□ 4	7.75	294	▼ 9	3.31	311	▼ 10	2.68
SPAIN		673	10	2.68	72	□ 13	1.55	297	▲ 8	3.35	304	▼ 11	2.62
BRAZIL		546	11	2.18	69	□ 15	1.49	152	▲ 13	1.71	325	▲ 9	2.80
TAIWAN		449	12	1.79	42	□ 21	0.91	182	▲ 11	2.05	225	▼ 13	1.94
FRANCE		417	13	1.66	86	□ 11	1.86	141	▼ 15	1.59	190	▼ 16	1.64
PORTUGAL		416	14	1.66	140	□ 8	3.02	115	▼ 17	1.30	161	▼ 18	1.39
TURKEY		412	15	1.64	41	□ 22	0.89	109	▲ 20	1.23	262	▲ 12	2.26
POLAND		363	16	1.45	33	□ 23	0.71	113	▲ 19	1.27	217	▲ 14	1.87
AUSTRALIA		323	17	1.29	62	□ 16	1.34	152	▲ 12	1.71	109	▼ 22	0.94
MALAYSIA		313	18	1.25	15	□ 30	0.32	96	▲ 22	1.08	202	▲ 15	1.74
NETHERLANDS		307	19	1.22	103	□ 10	2.22	125	▼ 16	1.41	79	▼ 27	0.68
ROMANIA		300	20	1.20	25	□ 26	0.54	97	▲ 21	1.09	178	▲ 17	1.54
CANADA		295	21	1.18	52	□ 18	1.12	147	▲ 14	1.66	96	▼ 24	0.83
SINGAPORE		289	22	1.15	123	□ 9	2.66	114	▼ 18	1.29	52	▼ 35	0.45
IRELAND		228	23	0.91	25	□ 25	0.54	67	▼ 26	0.76	136	▲ 19	1.17
SWITZERLAND		219	24	0.87	70	□ 14	1.51	81	▼ 23	0.91	68	▼ 28	0.59
CZECH REPUBLIC		193	25	0.77	19	□ 29	0.41	78	▲ 25	0.88	96	□ 25	0.83

single country, location of their institutions was scanned first. If 2 authors' institutions were located in China, then China's country scientific production frequency was increased by two. If the third author's institution was located in the USA, then USA's country scientific production frequency was increased by one.

It can be observed from Table 3 that China is by far the most productive country in hydroxyapatite and scaffold research although it was behind the USA in the first time period (1991-2009). Moreover, it can be noticed that scientific production of Iran in this topic increased rapidly over time. It's ranking jumped from 17 to 7 between the first and second time period, and from 7 to 3 between the second and third time period. Consequently, Iran is located at sixth place on overall rating of country scientific production. This is due to the fact that Vice-Presidency for Science and Technology Department of Islamic Republic of Iran, founded in 2006, has supported scientific researches with an annual budget of nearly 540 billion Iranian Rials (128 million USD) [90]. Furthermore, India, Brazil, Turkey and Poland can be shown as other countries whose country scientific production frequency rankings climb over time on this research area. On the other hand, Japan, the UK, France and Portugal can be shown as countries whose rankings fall over time on this research area.

Result of this bibliometric analysis on HA and scaffold research has revealed the fact that most of the scientific production in this research area consists of single country publications. Nevertheless, there exists a considerable amount of publications that were

Table 4. Country collaboration map (Top 25).

	Country 1		Country 2		Frequency
1	CHINA		USA		211
2	USA		SOUTH KOREA		75
3	UNITED KINGDOM		GERMANY		56
4	CHINA		JAPAN		46
5	CHINA		AUSTRALIA		43
6	CHINA		UNITED KINGDOM		43
7	USA		IRAN		42
8	CHINA		GERMANY		41
9	UNITED KINGDOM		USA		40
10	ITALY		SPAIN		38
11	UNITED KINGDOM		ITALY		37
12	ITALY		GERMANY		36
13	USA		ITALY		35
14	USA		GERMANY		32
15	SWITZERLAND		GERMANY		31
16	USA		JAPAN		30
17	USA		INDIA		28
18	USA		NETHERLANDS		27
19	CHINA		NETHERLANDS		26
20	INDIA		SOUTH KOREA		25
21	GERMANY		AUSTRALIA		24
22	CHINA		SOUTH KOREA		23
23	UNITED KINGDOM		SOUTH KOREA		22
24	USA		SPAIN		22
25	CHINA		SINGAPORE		21

created by international collaboration. These international collaborative publications were further analyzed, and country collaboration was mapped in Table 4. Country collaboration map shows that China – USA collaboration has the highest frequency (221) which is followed by USA – South Korea (75), UK – Germany (56) and China – Japan (46). It can be noticed that the top 10 countries in country scientific frequency also appears in the top 25 of country collaboration map. The USA is the most appeared country in country collaboration top 25 maps which are being followed by China, Germany and the UK.

Totally, 8752 publications emerged from 90 countries and 4582 institutions. As expected, several inter-institutionally collaborative publications were much higher than internationally collaborative publications. For publications that are co-authored by authors from different institutions, one point was given to each authors' institution. For example, if an article was co-authored by three authors from the same institution and one author from a second institution, 3 points were given to the first institution, and 1 point was given to the second one. Top 25 most productive institutes on the research field from all over the world were listed in Table 5. 8 institutes from China, 3 each from the USA, South Korea and Iran, 2 from Germany and 1 each from Singapore, Portugal, India, the UK, Malaysia and Japan shared the top 25 list. Indian Institute of Technology was ranked in the 9th position, but this does not worth anything. Because it was the integration of many institutes that are distributed all over the country. Not surprisingly, institutes from China were listed in the top 3. Sichuan University was the most productive institute for all three periods in this research field, which is followed by Central South University and Shanghai Jiao Tong University. With the exception of these three institutions Seoul National University from South Korea, the University of Michigan from the USA and the National University of Singapore from Singapore were the institutes having the highest scientific production. Furthermore, although Italy and Spain were ranked in fourth and 10th position respectively in-country scientific production list, no institutes from these countries entered the top 25 most productive institutes list.

In Table 6, published researches based on tissue engineering (TE) and bone tissue engineering (BTE), scaffold as an inseparable part of this technique, and porosity of scaffolds were given in three periods. Focusing on TE as a promising strategy for fixing bone defects has increased during the last three decades. This increase has been accelerated extremely throughout the last ten years, especially from 2015 to 2019. The number of publications between 2015and 2019 is 1055, which is almost twice of 539 published articles from 2010 to 2014. From 1991 to 2009, only 395 papers were published in TE/BTE filed. Whereas, in just five years these number has been increased by the rate of 36% to 540 articles. However, the highest increase rate was observed in the most recent period between 2015 and 2019. Research on Scaffolds has increased by the rate of 47% during only five years of the second period compared to 20 years of the first period, and published articles number with scaffold keywords has risen from 515 to 732. Nevertheless, only 8.5% increase rate has been observed in the third period compared to the years between 2010 and 2014. Moreover, porosity, which is one of the main characteristics of scaffolds, follows the same trend as a scaffold with approximately 47% increase rate from the first period to second; but the rate of research on porosity has even decreased during last five years compared to five years from 2010 to 2014.

The manufacturing methods used for the fabrication of scaffolds are summarized in Table 7. In the first period, which has last for 19 years, the tendency to use classical or traditional fabrication methods and additive manufacturing (AM) processes were almost the same; whereas, there was less intention to use electrospinning method. After 2009, prefer to use electrospinning has increased dramatically (more than three times) for the next five years. Rate of using AM has increased by 48% in the same period, while, the increase rate number was only 9% for classical scaffold fabrication methods. AM processes dominated the most recent period from 2015 to 2019. During these five years, using AM methods have increased to 353 cases compared to the preceding period. This increase is about 2.5 times of 147 articles published from 2010 to 2014. However, electrospinning and classical scaffold fabrication methods were implemented less than AM, especially traditional

Table 5. Top 25 most productive institutes.

				Scientific Production						
	INSTITUTES	REGION		1991-2019	1991-2009		2010-2014		2015-2019	
1	SICHUAN UNIV	CHINA		394	□	102	▲	141	▲	151
2	CENT S UNIV	CHINA		237	□	8	▲	78	▲	151
3	SHANGHAI JIAO TONG UNIV	CHINA		223	□	12	▲	85	▲	126
4	SEOUL NATL UNIV	SOUTH KOREA		184	□	71	▼	61	▼	52
5	UNIV MICHIGAN	USA		171	□	95	▼	41	▼	35
6	NATL UNIV SINGAPORE	SINGAPORE		168	□	68	▲	71	▼	29
7	TSINGHUA UNIV	CHINA		167	□	58	▼	54	▲	55
8	IMPERIAL COLL LONDON	UK		164	□	83	▼	55	▼	26
9	INDIAN INST TECHNOL	INDIA		164	□	8	▲	39	▲	117
10	ZHEJIANG UNIV	CHINA		163	□	21	▲	60	▲	82
11	UNIV ERLANGEN NURNBERG	GERMANY		153	□	22	▲	51	▲	80
12	DANKOOK UNIV	SOUTH KOREA		151	□	28	▲	87	▼	36
13	AMIR KABIR UNIV TECHNOL	IRAN		128	□	10	▲	45	▲	73
14	ISLAMIC AZAD UNIV	IRAN		124	□	2	▲	31	▲	91
15	MISSOURI UNIV SCI AND TECH	USA		113	□	19	▲	70	▼	24
16	UNIV PORTO	PORTUGAL		112	□	25	▲	34	▲	53
17	TOHOKU UNIV	JAPAN		110	□	40	▼	34	▲	36
18	WUHAN UNIV	CHINA		107	□	13	▲	37	▲	57
19	PEKING UNIV	CHINA		106	□	15	▲	42	▲	49
20	CHONBUK NATL UNIV	SOUTH KOREA		105	□	5	▲	52	▼	48
21	UNIV ILLINOIS	USA		103	□	33	▲	43	▼	27
22	SHANGHAI INST CERAM	CHINA		102	□	32	▲	33	▲	37
23	TECH UNIV DRESDEN	GERMANY		101	□	24	▲	42	▼	35
24	UNIV TEHRAN MED SCI	IRAN		100	□	6	▲	38	▲	56
25	UNIV MALAYA	MALAYSIA		97	□	0	▲	30	▲	67

processes. The increasing rate of using these two methods was 10.2% for electrospinning and less than 1% for classical methods. Table 8 displays usage of hydroxyapatite (HA), calcium phosphate (CaP), and tri-calcium phosphate (TCP) as ceramic biomaterials in literature. Among different bioceramics, application of HA was drastically higher than others during all three decades. Between the years 1991 to 2009, researchers, who were interested in HA have published 702 articles. Whereas, the number of studies

Table 6. Published articles with keywords tissue engineering, bone tissue engineering and porosity in three time periods from 1991 to 2019.

	1991-2009	2010-2014	2015-2019
tissue engineering, bone tissue engineering	395	540	1055
scaffold	515	732	795
porosity	240	353	325

Table 7. Published articles classification according to fabrication method of scaffold in three time periods from 1991 to 2019.

	1991-2009	2010-2014	2015-2019
Classical scaffold fabrication	98	107	109
Electrospinning	57	183	202
Additive manufacturing	99	147	353

Table 8. Published articles classification according to bioceramic type in three time periods from 1991-2019.

	1991-2009	2010-2014	2015-2019
Calcium phosphates (CaP)	192	211	225
Tri-calcium phosphates (TCP)	84	124	141
Hydroxyapatite (HA)	702	1000	1147

Table 9. Published articles that used different natural or synthetic polymers in HA composite scaffolds in three time periods from 1991-2019.

	Polymers	**1991-2009**	**2010-2014**	**2015-2019**
Natural Polymers	chitosan	121	178	244
	collagen	96	143	191
	gelatin	43	72	114
	alginate	17	29	60
	silk fibroin	24	50	96
	cellulose	9	24	48
	TOTAL	**310**	**496**	**753**
Synthetic polymers	polycaprolactone (PCL)	51	119	140
	poly(lactic-co-glycolic) acid (PLGA)	79	84	65
	poly lactic acid, polylactide (PLA)	21	56	74
	poly l lactic acid (PLLA)	29	55	36
	hydrogel	20	45	108
	polyurethane	8	30	34
	polyvinyl alcohol (PVA)	9	18	35
	polyamide (PA)	9	14	10
	polyethylene glycol (PEG)	14	9	16
	hyaluronic acid	7	13	19
	graphene	2	51	133
	TOTAL	**249**	**492**	**669**

using CaP and TCP it was only 192 and 84 respectively during the first 19 years period. A similar gap between usage of HA and two others also was observed in the second and third periods.

Further, it is clear from Table 8 that articles numbers, which introduced HA and TCP as biomaterials, were increasing by 42% and 47% in years 2010-2014 compared to the previous period. However, publications with CaP base biomaterials only experienced a nearly 10% increase in number. Comparing last period with preceding one, HA stands on top of most used materials list with 1147 articles; while, CaP and TCP were in second and third ranks with 225 and 141 articles respectively. Moreover, the increasing rate of using HA and TCP dropped to 15% and 14% respectively. Meanwhile, the CaP had the lowest increasing rate of 7% during the last five years.

The polymer is a biomaterial, which has been used frequently in many composite HA scaffolds. Polymers are divided into two groups, natural and synthetic, because of their origin. Table 9 shows published articles that used different polymeric biomaterials, either natural or synthetic, as the second phase of HA composite scaffolds in three periods during years 1991 to 2019. The data of Table 8 reveals that preference to employ natural or synthetic polymers were almost the same in all three periods, especially in the second period from 2010 to 2014. However, the tendency to use natural polymers was slightly higher than synthetic ones before 2010 and after 2014. The increase rate in using natural polymers was about 60% and 52% in the second and third periods respectively.

Meanwhile, the rate of increase for synthetic polymers were 98% and 36% in the same periods. Note that the first period was about 20 years while the second and third periods over five years. Therefore, there is a huge tendency to use polymer, both natural and synthetic, in HA composite scaffolds.

Eight thousand seven hundred fifty-two research items related to hydroxyapatite and scaffold were published in a wide range of 1298 publication sources. One thousand one hundred fifty-seven publication sources out of 1298 contained less than ten publications throughout the period from 1991 to 2019. The top 25 most productive publication sources in this research area were illustrated in Figure 2. These 25 publication sources contained 3894 research items which correspond to 44.49% of total scientific production. Journal of Biomedical Materials Research Part A, which internationally publish studies of the preparation, performance, and evaluation of biomaterials, was ranked as the most productive publication source with 447 research items which corresponds to 5.11% of total scientific production. Materials Science and Engineering: C which includes topics at the interface of materials engineering and biomedical science occupied the second rank of the most productive publication sources (408; 4.66%), which is followed by Journal of Materials Science: Materials in Medicine (329; 3.76%), Acta Biomaterialia (298; 3.40%), and Biomaterials (283; 3.23%).

The top 10 publications that have the highest number of citations among 8752 were displayed in Figure 3. The top cited publication is Karageorgıou V., 2005, Biomaterials, and it was cited 2901 times in total. The following second and third publications are Hartgerink J.D., 2001, Science (2528 times) and Deville S., 2006, Science (1015 times) respectively. It can be noticed from the figure that the top 10 most cited articles were published in 4 journals. These are Biomaterials Journal (5 articles), Science Journal (2 articles), Acta Biomaterialia Journal (2 articles) and Clinical Orthopaedics and Related Research Journal (1 article).

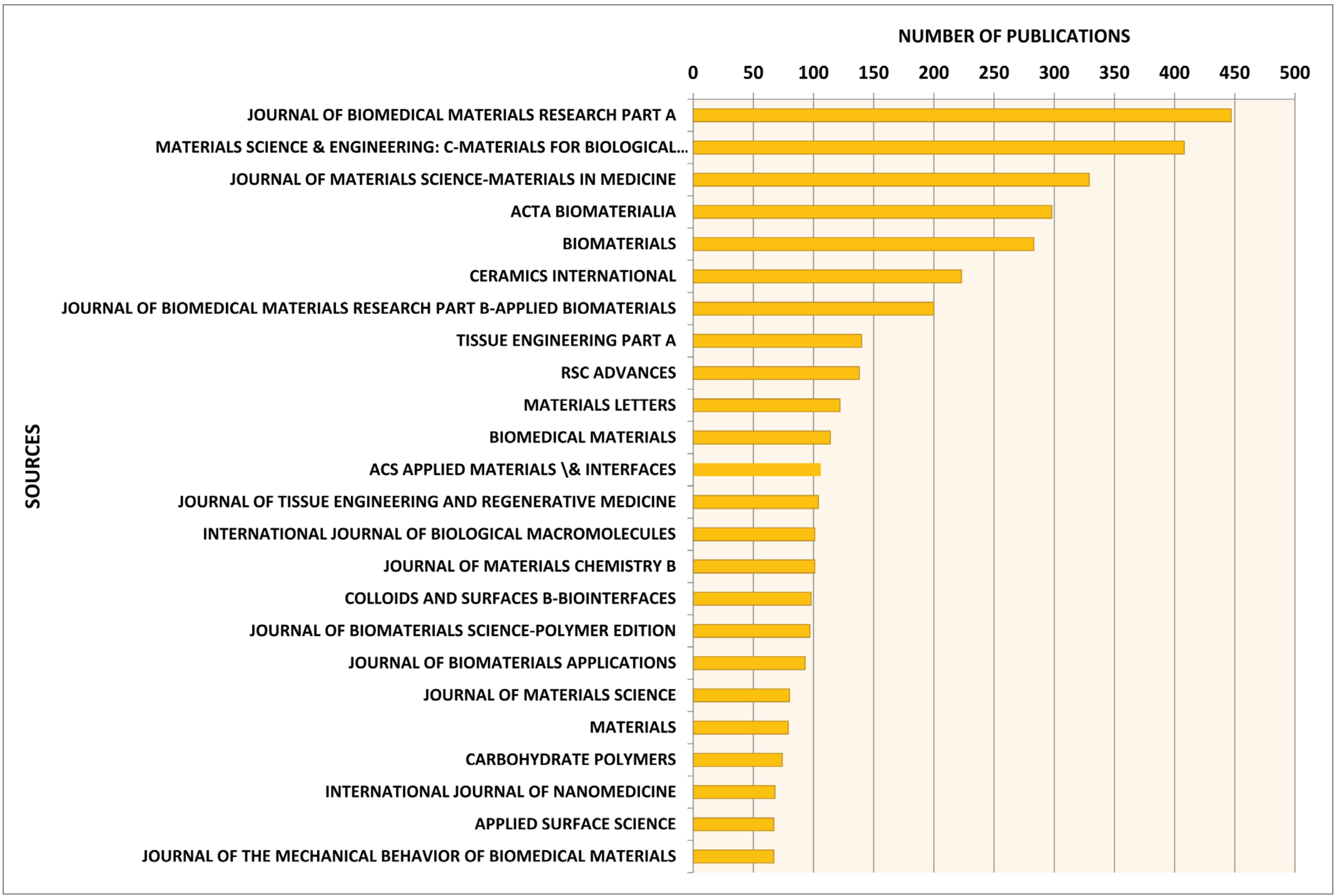

Figure 2. Most productive publication sources.

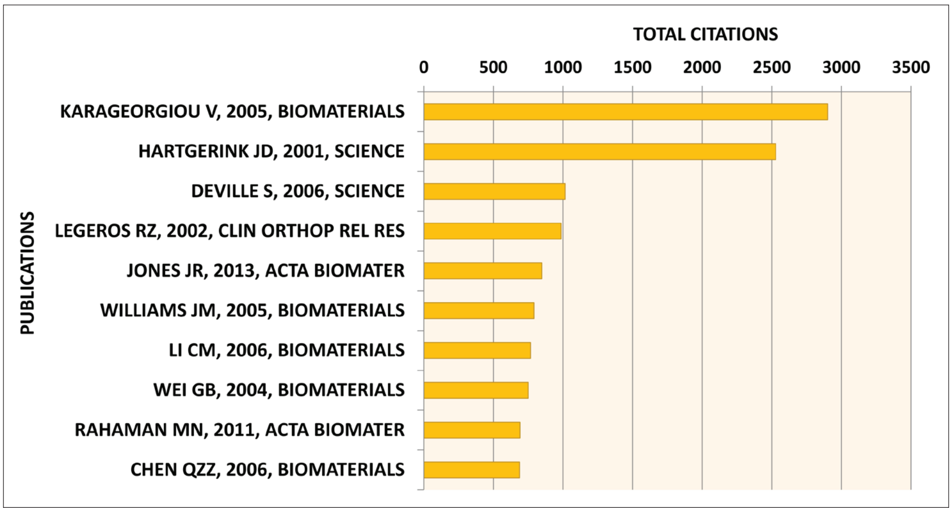

Figure 3. Most cited publications.

4. Summary

This bibliometric study portrays the global trends in scientific researches related to HA-based scaffolds and contributes to highlighting some important points of this research field during the past 29 years from 1991 to 2019. First, the results revealed that the tendency to use HA-based scaffolds and TE to regenerate or restore defected tissues had been increased dramatically throughout the explored period due to shortcomings of autografts (harvest tissue from the patient's body), allograft (harvest tissue from a donor's body), or using sole biomaterials as traditional methods. Second, there is a significant rise in the number of articles, which used AM methods to develop scaffolds. The AM allows having better control over geometry, porosity, pore size, and interconnectivity of scaffolds. These features affect the performance of scaffolds in the growth and development of tissues. However, achieving the perfect control over geometrical and structural features of scaffolds is a matter of challenge up to present time because of the limitations of used devices, such as resolution or printable materials. Third, owing to desirable properties of HA, such as similarity to inorganic part of natural bone, biocompatibility, bioactivity, osteoconductivity, as well as high compressive strength, application of HA in making scaffolds has increased during the last decade. Moreover, to overcome the weak features of HA scaffolds, like brittleness, they reinforced by natural or synthetic polymers to form composite scaffolds with higher toughness [9].

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