Research hotspots and trends of microRNA in periodontology and dental implantology: a bibliometric analysis

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Background: Periodontal disease is a leading cause of tooth loss, and microRNA (miRNA) has been shown to regulate various biological processes. This study aimed to quantitatively analyze the literature related to miRNA in periodontology and dental implantology and summarize the research hotspots and trends in this field.

Methods: Literature records from 1985 to 2020 were obtained from the Web of Science Core Collection database. After manual selection, the data was used for cooperative network analysis, keyword co-occurrence analysis, and reference co-citation analysis and visualized by CiteSpace.

Results: A total of 287 papers were analyzed between 2007 and 2020, and more than 95% of them were published in the past decade. The largest number of publications were from China, followed by the USA and Japan. The direct cooperation among the productive institutions was not close. At present, most of the research belongs to the discipline of dentistry, oral surgery, cell biology, and molecular biology. Literature clusters generated by reference co-citation analysis and keyword co-occurrence network showed that previous studies mainly focused on four hotspots: periodontal ligament stem cells (PDLSCs), the pathological process of periodontitis, osteogenic differentiation/bone regeneration, and the competing endogenous RNA (ceRNA) network.

Conclusions: The therapeutic potential of miRNA in promoting bone formation and how the ceRNA network contributes to miRNA regulation at a deeper level have become the two main research trends of this field.

Keywords: MicroRNA (miRNA); periodontics; dental implants; bibliometric analysis; CiteSpace

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Introduction

The Global Burden of Disease study has shown that the incidence of severe periodontal disease ranks 11th in the world, affecting more than 700 million people (1). Periodontitis, the most common periodontal disease, is a chronic inflammatory disease induced by plaque and characterized by progressive loss of supporting bone tissue (2). It is the leading cause of tooth loss and is considered one of the two most significant dental health threats (3). Due to its high success rate and relatively few biological complications, a dental implant has become a popular option for replacing missing teeth over the past

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few decades. A study predicted that as many as 23% of adults would choose implants to replace missing teeth by 2026 (4). However, similar to natural teeth, peri-implant tissue can develop a pathological disease akin to periodontitis, that is, peri-implantitis. Many studies have shown that patients with periodontitis have a higher incidence of peri-implantitis than those without, and there is strong evidence that shows the medical history of periodontitis is a risk factor for peri-implantitis (5).

MicroRNA (miRNA) is a class of single-stranded non-coding RNA with about 22 nucleotides. Their primary form is encoded by genomes in the nucleus and then transported to the cytoplasm for further processing to form mature miRNA. In most cases, miRNA participates in the post-transcriptional regulation of gene expression by binding to the 3' untranslated region of the target messenger RNA (mRNA) to induce mRNA degradation or inhibition (6). Because of the limited complementarity between miRNA and mRNA, a single miRNA can target many mRNAs, and different miRNAs can also target a single mRNA. There are more than 300 kinds of miRNAs in mammals. However, it is estimated that miRNA can regulate about 60% of gene expression (7), including several physiological processes, such as development, differentiation, and apoptosis (6). In recent years, there have been increasing studies on the role of miRNA in the pathological process of inflammatory diseases, such as periodontal disease, as well as in the bone formation and remodeling (8-10).

Bibliometric analysis has been widely used across many research fields (11-13). Through the quantitative analysis of a certain discipline's literature, we can construct its intellectual structure and explore its development trend. This method helps researchers find the scope of research fields and predict future research directions. CiteSpace is an information visualization software for measuring and analyzing scientific literature data (14). It can present knowledge networks in the field of science in the form of graphs, visually show the panorama of information in the field of scientific knowledge, and help researchers identify key literature, research hotspots, and frontier directions in a specific scientific field (14). To the best of our knowledge, the current analysis is the first bibliometric analysis in this field. We aimed to describe miRNA's scientific achievements in periodontology and dental implantology so far to identify research hotspots and trends and guide future research.

Methods

Data acquisitions

Literature data were retrieved from the Web of Science Core Collection database, which was widely applied in bibliometric research using the advanced search strategy. The search query was "TS = ((mi*rna* OR mir) AND (periodont* OR dental implant* OR peri-implant* OR periimplant*))". The restricting strategy of results was: (I) document types (article or review); (II) languages (English); (III) timespan (1985–2020); (IV) index (Science Citation Index Expanded, Current Chemical Reactions, Index Chemicus). To avoid bias caused by daily database updates, literature retrieval was completed within a single day. Two reviewers independently screened the titles and abstracts of search results to exclude literature not related to periodontology or dental implants. A third reviewer screened any literature that sparked disagreement between the two reviewers to decide whether it would be included or not. The records were exported in the plain text file format of "Full Records and Cited References". Each literature record contained relevant information needed for analysis, such as title, author, keywords, abstract, and so on.

Statistical analysis

Web of Science's *Results Analysis* and *Citation Report* were used for analyzing the publications' quantity in different views, such as years, journals, and authors. Then the downloaded data was imported into CiteSpace (version 5.7 R2) for further analysis. Record screening results determined the final time span of data, that is, 2007–2020. The time slice was 1 year. We selected three node types, *Author*, *Institution*, and *Country*, for cooperative network analysis. *Keyword* was selected for co-occurrence and burst analysis. *Reference* was selected for co-citation analysis. To improve the analysis efficiency and optimize the visualization results, we choose different selection criteria and image pruning types for different node types (*Table 1*). The rest of the parameter settings remained at the default. Besides, we conducted discipline and journal analysis using the dual-map overlay of CiteSpace.

Results

Temporal distribution of the literature

A total of 336 papers were retrieved. After screening,

Table 1 The configuration of CiteSpace

Node types	Time slicing	Selection criteria	Pruning
Author			
Institution		Top 100%	No Pruning
Country	2007–2020; years per slice: 1		
Keyword		g-index; k=25	Pathfinder; Pruning the merged network
Reference			

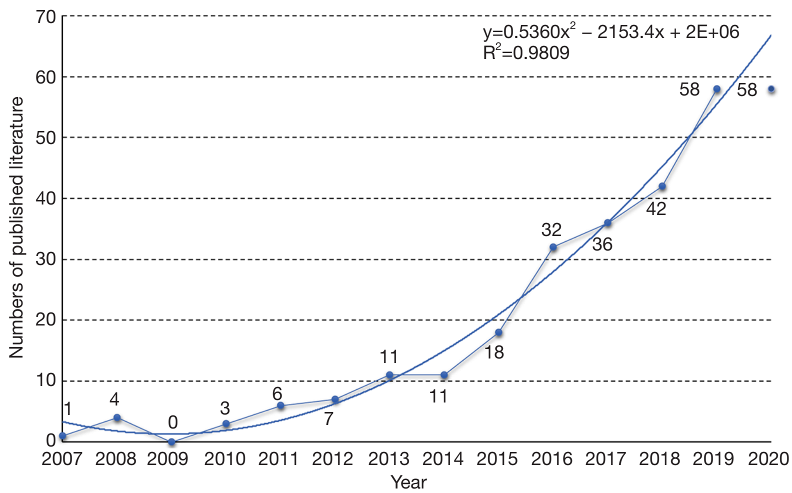

Figure 1 The total number of published literature over time.

287 papers were included from 2007 to 2020, consisting of 251 articles and 36 reviews. As shown in *Figure 1*, there were fewer than 10 papers per year from 2007 to 2012. From 2014, with the gradually deepening study in this field, the number of published papers has continued to increase. The citation frequency of papers in this field has increased annually; the largest growth was in 2019 [1,009], with an increase of 46.02% compared with the previous year [691] (*Figure 2*).

Discipline and journal analysis

A total of 287 papers were published in 145 journals. The journal with the largest number of publications was the *Journal of Dental Research* [19]. The vast majority of journals [128] published 3 or fewer papers, of which 100 journals published only 1 paper. *Table 2* shows the 8 journals with the largest number of publications. As shown in *Figure 3*, a dual-map created by CiteSpace shows the result of discipline and journal analysis. The left side represents the citing literature's journal distribution, and the right represents the journal distribution of the cited literature. The more papers published in the journal, the longer the ellipse's vertical axis; the more the number of authors, the longer the transverse axis. Studies from *Molecular/Biology/Immunology* most frequently cited studies from *Molecular/Biology/Genetics*. Generally speaking, this field's current research is mainly focused on *Dentistry*, *Oral Surgery and Medicine*, *Cell Biology*, *Biochemistry, and Molecular Biology*, *Medicine*, *Research and Experimental*, and other categories.

Cooperative network analysis

In the cooperative network analysis diagram, the node represents a country, institution, or author. The size of the node represents the number of publications. The color of the connection between the nodes represents the year of the first cooperation between the nodes.

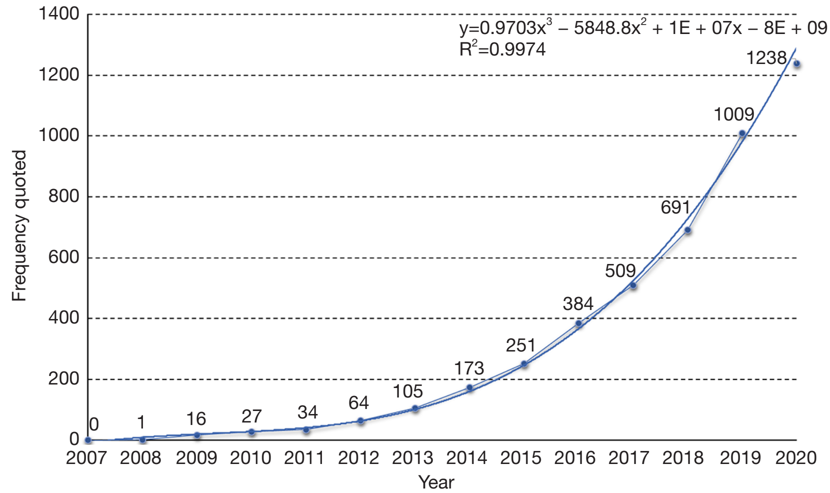

Figure 2 Frequency quoted over time.

Table 2 Top 8 journals with the largest number of publications

No.	Journals	Count (N)	% of 287	Categories	2019 IF
1	*Journal of Dental Research*	19	6.62	Dentistry, Oral Surgery & Medicine	4.914
2	*Journal of Periodontal Research*	12	4.18	Dentistry, Oral Surgery & Medicine	2.926
3	*Archives of Oral Biology*	10	3.48	Dentistry, Oral Surgery & Medicine	1.931
4	*Journal of Periodontology*	9	3.14	Dentistry, Oral Surgery & Medicine	3.742
5	*Journal of Cellular Physiology*	8	2.79	Dentistry, Oral Surgery & Medicine	5.546
6	*International Journal of Molecular Sciences*	7	2.44	Biochemistry & Molecular Biology Chemistry, Multidisciplinary	4.556
7	*Journal of Cellular Biochemistry*	7	2.44	Biochemistry & Molecular Biology	4.237
8	*Oral Diseases*	7	2.44	Dentistry, Oral Surgery & Medicine	2.613

Distribution of countries/regions

The 287 papers were from 36 countries, more than half of which were from China, followed by the United States. *Table 3* shows the 8 countries/regions with the largest number of publications. The countries/regions cooperative network created by CiteSpace is shown in *Figure 4*. China and the USA, as the 2 countries with the most publications, had the most cooperation. The countries/regions that cooperated closely with China were mainly distributed in Asia, including Japan, India, and South Korea, while those with close cooperation with the USA were distributed in Europe and America, including Germany, Brazil, and Mexico.

Distribution of institutions

Since most institutions had less cooperation with others, the network was sparse. We set CiteSpace to show only the largest subnet. As shown in *Figure 5*, although institutions that have published more than 10 papers were in this sub-network, cooperation among institutions with many publications was still not extensive. For example, there was no direct cooperation among the top 3 institutions: Shandong University, the Fourth Military Medical University, and Sichuan University.

Distribution of authors

According to Web of Science's statistical results, a large

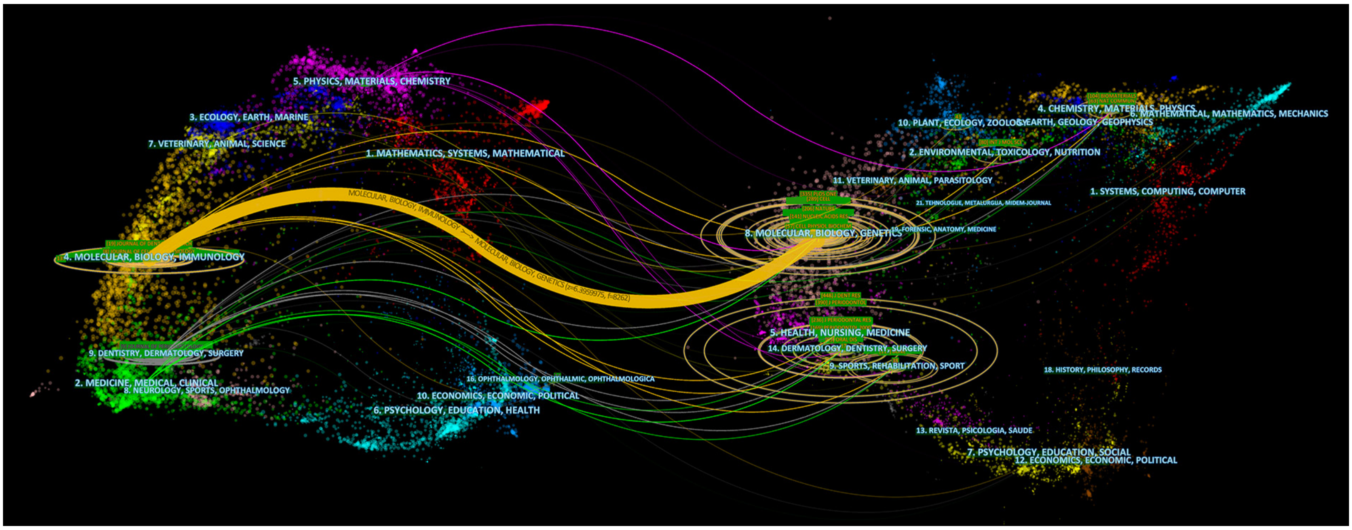

Figure 3 The dual-map overlay of journals related to the miRNA in periodontology and dental implantology. Left side: citing journals. Right side: cited journals. The color of links distinguished the disciplinary of the source.

Table 3 Top 8 productive countries/regions related to the miRNA in periodontology and dental implantology

No.	Country/regions	Count (n)	% of 287	H-index	Average citations per item
1	China	168	58.54	25	11.3
2	USA	62	21.60	21	19.4
3	Japan	19	6.62	10	18
4	Italy	16	5.58	9	13.63
5	Brazil	11	3.83	6	27.73
6	Germany	9	3.14	6	22.33
7	India	9	3.14	5	6.33
8	South Korea	8	2.79	5	18.38

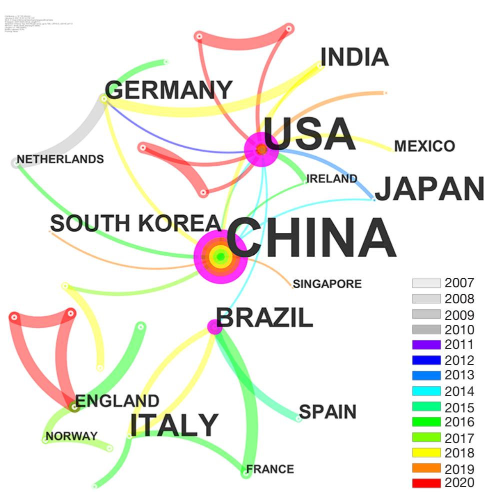

Figure 4 Cooperation network map of countries/regions.

number of authors [1,048] had published only 1 paper, and only 28 had published 5 or more papers. Among them, Wei FL and Nares S were the only 2 authors who had published more than 10 papers in this field. From the author cooperation network (*Figure 6*), it can be seen that there is still a lack of direct cooperation between the productive authors in this field, like the institutional cooperation network.

Burst keywords analysis

After preliminary extraction and sorting, 1,402 keywords were obtained from 287 papers by CiteSpace. *Table 4* lists the 10 keywords with the highest frequency. To obtain high-frequency keywords that can better reflect the research hotspots and trends, we further adjusted the CiteSpace

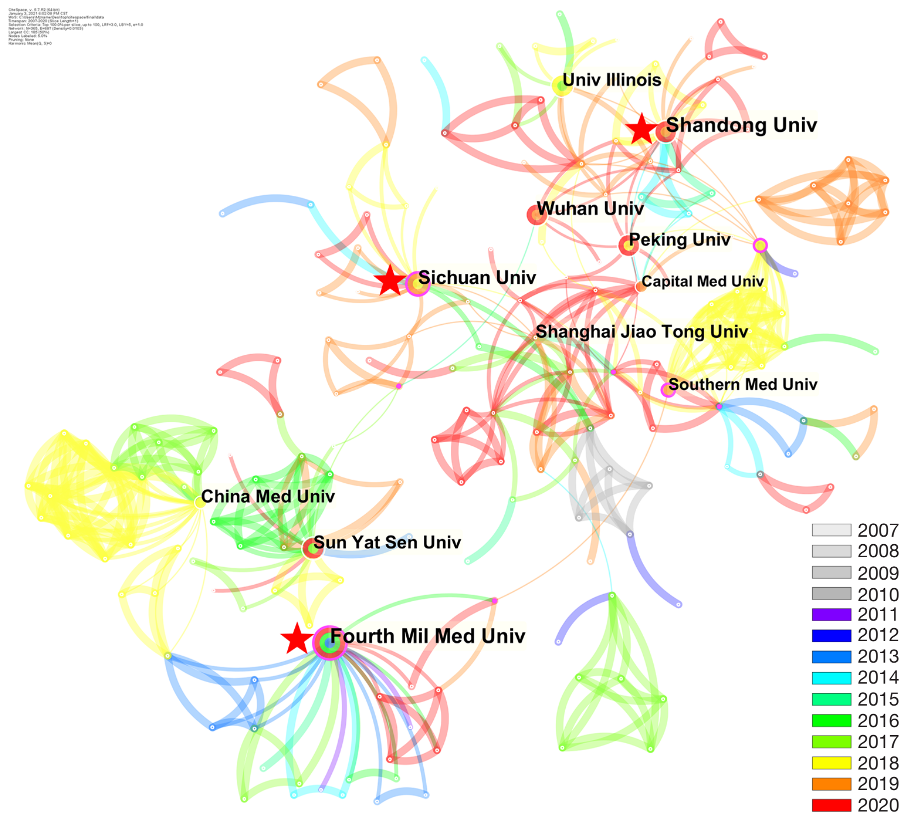

Figure 5 Cooperation network map of institutions.

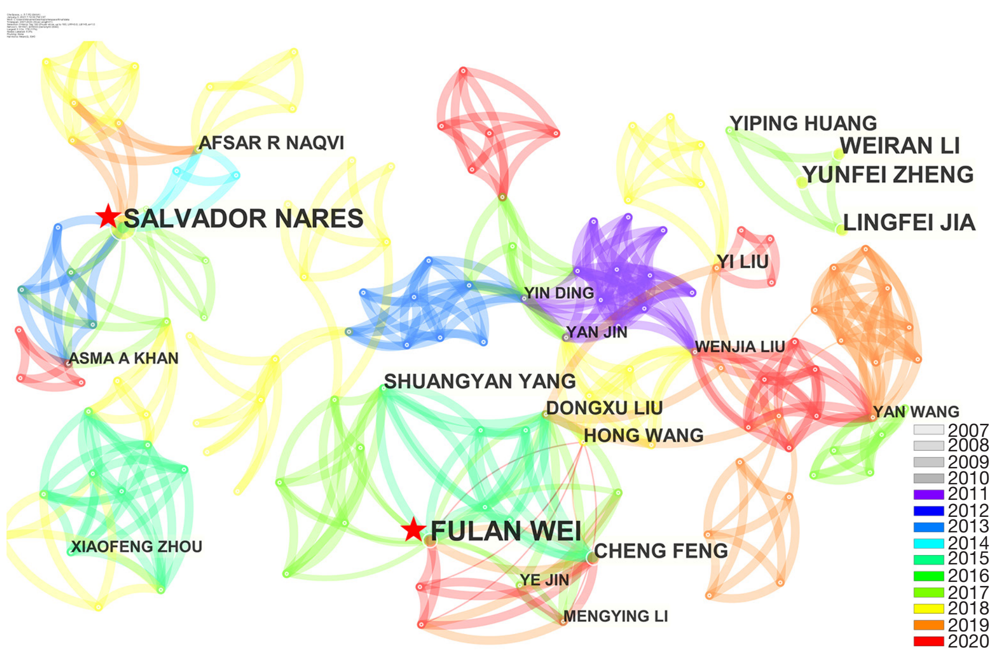

Figure 6 Cooperation network map of authors.

Table 4 Top 10 frequent keywords related to the miRNA in periodontology and dental implantology

No.	Frequency	Keyword
1	143	MicroRNA
2	107	Expression
3	72	Periodontitis
4	61	Osteogenic differentiation
5	49	Differentiation
6	49	Inflammation
7	48	Proliferation
8	40	Gene expression
9	37	Mesenchymal stem cell
10	36	Disease

parameters, selected 20 keywords with the highest citation in each time slice to draw the keyword co-occurrence network (*Figure 7*), and determined 15 keywords with the highest burst strength (*Figure 8*). The keyword *microarray* was one of the longest-lasting burst keywords. *Regeneration*, *periodontal ligament stem cell*, *osteogenesis*, and others were the latest burst keywords in the past 3 years.

Reference co-citation analysis

When two articles were cited by a third article together, they then constituted a co-citation relationship. The higher the intensity of co-citation, the stronger the relevance of the two articles and the closer the research topics. *Tables 5,6* and *Figure 9* list the publications with

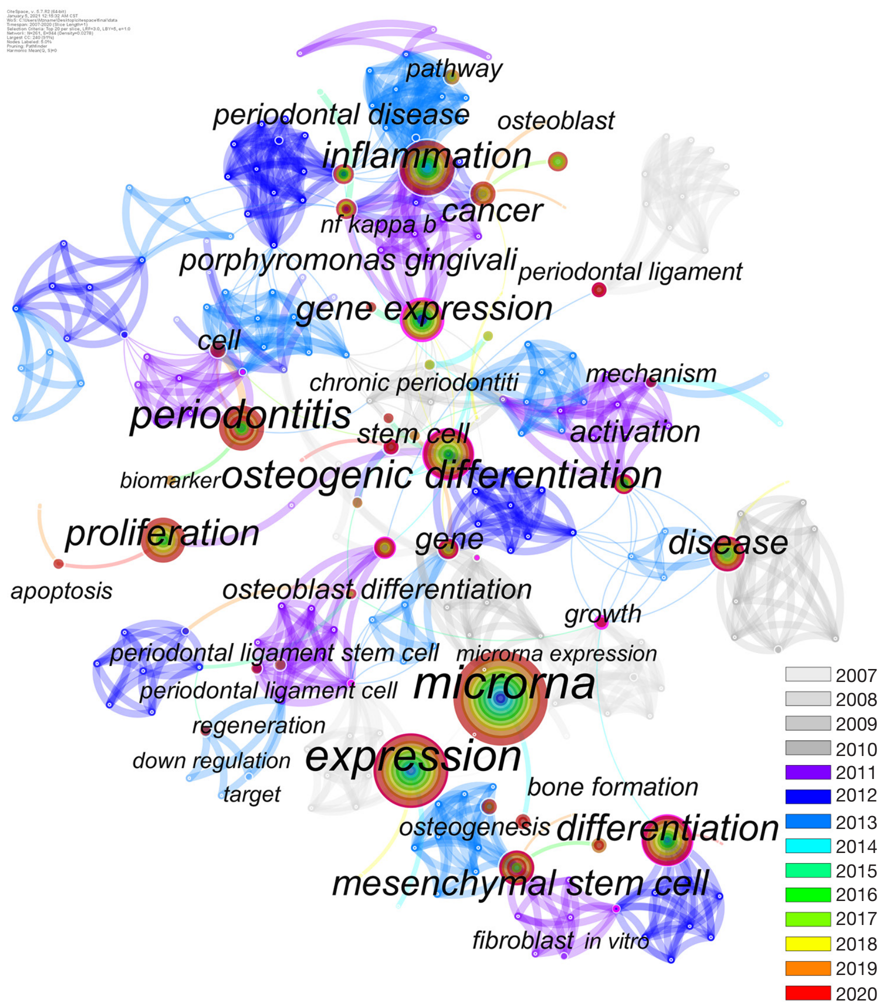

Figure 7 Co-occurrence network map of keywords.

Figure 8 Top 15 keywords with the strongest citation burst.

Table 5 Top 5 cited citations with the highest co-citation count

No.	Count	Year	Cited references
1	27	2012	Stoecklin-Wasmer C, 2012, *J Dent Res*, V91, P934
2	23	2014	Ogata Y, 2014, *J Oral Sci*, V56, P253
3	22	2015	Wei FL, 2015, *Stem Cells Dev*, V24, P312
4	21	2015	Motedayyen H, 2015, *J Periodontol*, V86, P1380
5	21	2011	Xie YF, 2011, *Int J Oral Sci*, V3, P125

the highest co-citations, betweenness centrality (BC), and burst strength. The distribution of the largest 8 literature clusters with close research topics on the timeline is shown in *Figure 10*. The nodes with a red ring represent the literature with high burst strength. The largest cluster was *#0 periodontal ligament/stem cells/bone formation*. The latest 2 clusters were *#1 osteogenic differentiation/angiogenesis/microRNA* and *#6 circular RNAs/cytokines/microRNA sponges*. The most representative keywords for each cluster under different algorithms are displayed in *Table 7*.

Discussion

Based on bibliometrics, this study visualized and analyzed the research trends of miRNA in periodontology and dental implantology using CiteSpace, and discussed the bibliometrics characteristics in this field. We retrieved a total of 287 papers that met the study requirements. The first paper was published in 2007. However, the research activity in this field had remained at a low level until 2012. From 2013 onwards, the annual number of relevant publications has exceeded 10, and the citation frequency has been more than 100, showing a steady annually increasing trend. This may be related to researchers' increasing attention to gene regulation in tissue development and disease pathology.

By analyzing the publications' disciplines and journals, researchers can understand the discipline distribution of the research in this field, track research progress, and choose more appropriate journals when submitting papers. In the dual map of journals and disciplines (*Figure 3*), the

Table 6 Top 5 cited citations with the highest betweenness centrality

No.	Centrality	Year	Cited references
1	0.22	2011	Lee YH, 2011, *Biocell*, V35, P0
2	0.21	2011	Nahid MA, 2011, *Infect Immun*, V79, P1597
3	0.18	2015	Kebschull M, 2015, *Periodontol* 2000, V69, P201
4	0.18	2015	Chang ML, 2015, *In Vitro Cell Dev-An*, V51, P797
5	0.16	2009	Nahid MA, 2009, *J Biol Chem*, V284, P34590

References	Year	Strength	Begin	End	2007–2008
Nahid MA, 2009, J BIOL CHEM, V284, P34590, DOI	2009	3.19	2011	2014	
OConnell RM, 2007, P NATL ACAD SCI USA, V104, P1604, DOI	2007	3.13	2011	2012	
Huang J, 2010, STEM CELLS, V28, P357, DOI	2010	2.86	2011	2013	
Nahid MA, 2011, INFECT IMMUN, V79, P1597, DOI	2011	4.03	2012	2016	
Xie YF, 2011, INT J ORAL SCI, V3, P125, DOI	2011	8.47	2013	2016	
Lee YH, 2011, BIOCELL, V35, P0	2011	5.61	2013	2016	
Stoecklin-Wasmer C, 2012, J DENT RES, V91, P934, DOI	2012	6.86	2014	2017	
Hung PS, 2010, J DENT RES, V89, P252, DOI	2010	3.55	2014	2015	
Xie YF, 2013, J INFLAMM-LOND, V10, P0, DOI	2013	3.06	2014	2018	
Perri R, 2012, JDENT RES, V91, P33, DOI	2012	4.47	2015	2017	
Li CX, 2012, MOL MED REP, V5, P1340, DOI	2012	3.09	2015	2017	
Krzeszinski JY, 2014, NATURE, V512, P431, DOI	2014	3.26	2016	2017	
Ogata Y, 2014, J ORAL SCI, V56, P253, DOI	2014	3.77	2018	2020	
Chen N, 2016, J DENT RES, V95, P1425, DOI	2016	3.4	2018	2020	
Hajishengallis G, 2015, NAT REV IMMUNOL,V15, P30, DOI	2015	2.96	2018	2020	

Figure 9 Top 15 references with the strongest citation bursts.

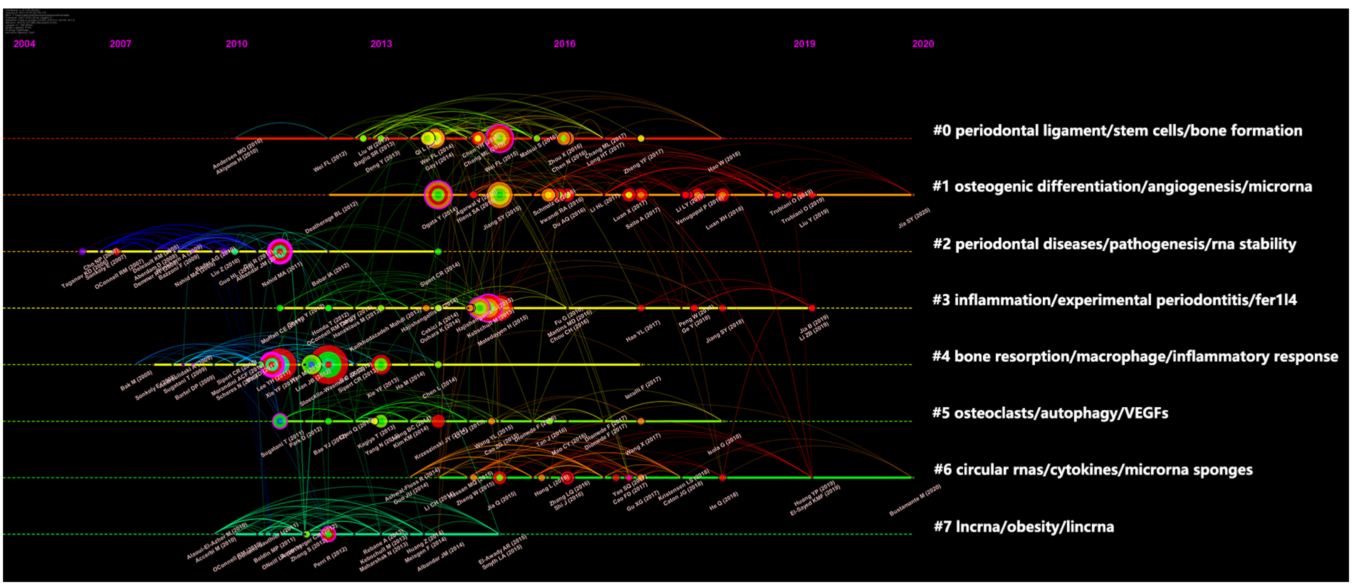

Figure 10 Co-citation network map of references on the timelines.

Table 7 Major clusters of co-cited references

Cluster ID	Size	Silhouette	Mean (year)	Label (LSI)	Label (LLR)	Label (MI)
0	51	0.91	2014	Periodontal ligament	Periodontal ligament	Tooth development
1	50	0.888	2017	Periodontitis	Osteogenic differentiation	Chitosan hydrogel
2	36	0.976	2009	Inflammation	Periodontal diseases	Periodontal diseases
3	35	0.861	2014	Osteogenic differentiation	Inflammation	Experimental periodontitis
4	33	0.902	2011	Fibroblasts; inflammation	Bone resorption	Bone resorption
5	32	0.881	2014	Osteogenesis	Osteoclasts	Autophagy
6	32	0.972	2016	Osteogenic differentiation	Circular RNAs	Cytokines
7	31	0.943	2012	Circular RNA	LncRNA	LncRNA

LSI, Latent Semantic Index; LLR, Log-likelihood ratio; MI, mutual information.

journal distribution of citing literature is on the left side, representing the major disciplines of the target field and can be regarded as the application of the target field. On the right is the journal distribution of the cited literature, representing the disciplines mainly cited in the target field and can be regarded as the fundamental of the target field. It is worth noting that the discipline analysis also revealed the areas that have attracted less attention from researchers. For example, in *Materials Science*, Palmieri found that the ability of Bio-oss to promote bone formation may be related to osteoblast regulation at the miRNA level and positive regulation of BMP-4 (15). Li designed a miRNA-activated scaffold composed of miR-21 nanoparticles and Bio-oss particles to accelerate the regeneration of alveolar bone from 3 months to 2 weeks after tooth extraction (16).

Katz and Martin defined scientific cooperation as researchers collaborating with the common purpose of producing new scientific knowledge (17). The scientific cooperation mentioned in this study refers to the simultaneous signing of different authors, institutions, or countries/regions in a paper, which is considered a cooperative relationship. Cooperative network analysis shows that the productive authors and institutions in this field each have many collaborators, but they lack direct cooperation with each other. This may be related to their ability to conduct strong independent research. They may already have the skills of an excellent partner that others are looking for, which negates the need to look for more cooperation actively. When evaluating the importance of nodes in the network, sociality is as important as the academic output. Sociality is considered to play an important role in knowledge networks because it may integrate different research groups' results. The parameter of BC is important for evaluating sociality. Nodes with a high BC value (BC >0.1) usually connect 2 or more large node groups. For example, Southern Medical University (BC =0.18) connects Xi'an Jiaotong University and the University of Michigan.

Productive research groups tend to pursue specific research topics. For example, Wei FL from Shandong University mainly studied the effect of miRNA on osteogenic differentiation of periodontal ligament stem cells (PDLSCs) under mechanical force and its possible mechanism (18-20). Their recent research further proposed that long non-coding RNAs (lncRNAs) and circular RNA (circRNAs) regulate miRNAs through the competing endogenous RNA (ceRNA) network to exert the effects mentioned above (21,22). This (21) is also the most cited article of Shandong University. The Fourth Military Medical University's research is related to the osteogenic differentiation of bone marrow mesenchymal stem cells (23-26). Based on exploring the role of miRNA, they developed a new type of titanium implant with miRNA on the surface and confirmed that this new material could promote osteogenesis (24). Nares from the University of Illinois is another author who has published more than 10 papers, which mainly studied the effect of viral miRNA on human oral gene expression. He reviewed the role of miRNAs in human periodontal disease (27), pulp disease (28), endodontic periapical disease (29), oral cancer (30), and other diseases and suggested that they may be related to inflammation (31). Differences in researcher interests may also contribute to the lack of direct collaboration between research groups. Personal early research experience may be the main reason for the difference in research interest, especially for those influential authors. Zeng found that the scientists with low topic switching probability in early career usually have the high average citation per paper, and the higher the switching probability, the lower the overall productivity they have (32). In addition, the institutions' research conditions and the funding's focus may also lead to differences in research interests. For example, researchers from hospitals often have easier access to tissue specimens and clinical data than those from institutes or laboratories.

Researchers often cite papers of previous researchers in later publications, which are listed as references. Over time, a network of related literature with similar research topics is formed. The literature network is composed of different clusters, and CiteSpace forms the label of each cluster by selecting representative keywords from citing literature. By analyzing the citation network and keywords in the temporal dimension, we can determine the research hotspots and trends of a specific period to determine the rise, flourishing, and decline of specific research clusters. In the timeline (*Figure 10*), the more the number of papers in a cluster, the more important the cluster is, and the higher its position in the figure. Through the analysis of the keywords of each cluster and the top papers in each cluster, in the past decade, the research hotspots of miRNAs in periodontology and dental implantology have mainly focused on the following four aspects.

Periodontal Ligament and PDLSCs

Unsurprisingly, periodontal ligament and stem cells are the two representative keywords of this field's largest cluster. They represent the primary materials used in research in this field. Seo first described PDLSCs in 2004 (33). They are pluripotent stem cells present in periodontal ligaments that can be easily isolated by non-invasive procedures such as standard subgingival scaling and root planing or from the root surface of isolated teeth (34). The PDLSCs can proliferate in heterogeneous culture medium, maintaining their morphological characteristics, markers related to pluripotency, and normal karyotype, and there has been no sign of senescence of PDLSCs cultured for 15 generations (34). The convenient way of gathering materials and this new culture method have laid a good foundation for the research of PDLSCs. The osteogenic differentiation potential of PDLSCs, especially the osteogenic differentiation induced by orthodontic force, also makes it the most commonly used research material in this field. Wei FL took the lead in sequencing the changes in the miRNA expression profile of human PDLSCs under the action of mechanical tensile force and identified 53 miRNAs with significantly different expression levels (18). Among these miRNAs, miR-21 has been one of the research hotspots. Wei demonstrated that miR-21 mediates osteogenic differentiation of human PDLSCs induced by stretch in 2015 (20) and later found that this regulation may be related to targeting Smad5 (35). Chen N's study in mice confirmed the role of miR-21 in orthodontic tooth movement (10) and received continuous attention in the following 2 years. Additionally, miR-21 has been found to affect down-regulating inflammation and inhibiting periodontitis (36). Due to the role of miR-21 in inflammation and osteogenic differentiation, Geng prepared a SrHA/miR-21 composite coating and applied it to the titanium surface to enhance osseointegration and bone-implant bonding strength (37).

In addition to PDLSCs, other types of stem cells have also been applied to research in this field. For example, Deng found that miR-31 negatively regulates bone marrow mesenchymal stem cells' osteogenic differentiation by targeting Satb2 (38). Gay I studied changes in the miRNA expression profile of gingival stem cells cultured under osteogenic induction conditions (39), and Qi used immortalized PDLSCs to discover that miR-132 can regulate fluid shear stress-induced osteogenic differentiation through the mTOR signaling pathway (40).

Pathological process of periodontitis

From the labels of cluster 2 to cluster 5, it is obvious that these groups of papers mainly studied the pathogenesis of periodontitis, and the research focused on two key points: inflammation and bone loss. The papers of Xie (41), Stoecklin-Wasmer (42), and Lee (43) had high burst strength and co-citation counts, which means that their research received much attention during a certain period. Their research was groundbreaking and sequenced miRNA profiles in periodontitis patients and healthy periodontal tissues using microarray and verified the results by reverse transcription-polymerase chain reaction (RT-PCR). It is worth noting that, as highlighted by Kebschull (44), the specimens used in these studies contained all the cellular components in their tissue biopsy specimens. Therefore, it is impossible to ascertain whether miRNA expression changes result from actual transcriptional changes or specific cell proliferation/apoptosis, or both. Nevertheless, their findings pointed to some potentially valuable miRNAs, which greatly helped later researchers choose their research goals.

The miRNA miR-146 was a hotspot in these researches. Nahid established a mouse model of periodontal pathogen multi-bacterial infection and observed a significant increase in miR-146a in periodontal tissue (45). Motedayyen found that the increased expression of miR-146a in patients with chronic periodontitis was positively correlated with inflammation's clinical parameters (46). Some studies have shown that miR-146a may regulate the pathological process of periodontitis through its interaction with nuclear factor kappa light chain enhancer of activated B cells (NF-κB): on the one hand, miR-146a itself is regulated by the activation of NF-κB; on the other hand, miR-146a negatively regulates the NF-κB pathway by down-regulating IRAK1/TRAF6 (44). Besides, the level of miR-146a in the saliva of patients with periodontitis was higher than those in the control group and is expected to be a reliable, non-invasive biomarker for the diagnosis prognosis of periodontitis, especially in diabetic patients with periodontitis (47). Sanada down-regulated the expression of inflammatory cytokine genes in mice's periodontal tissue by continuous intravenous administration of miR-146a, which is considered a potential treatment (48). The miRNA miR-155 is another research hotspot. Like miR-146a, miR-155 has been found to interact with the NF-κB pathway (44) and has a potential diagnostic value (47,49). Recent studies have shown that the Akt2/miR-155-5p/DET1/c-Jun axis can promote M2 polarization of macrophages and save bone loss caused by periodontitis, which is expected to become a new potential way to treat periodontitis (50).

Osteogenic differentiation and bone tissue regeneration

The average year of cluster 1 was 2017, which is consistent with the year when the latest burst keywords (such as *regeneration* and *osteogenesis*) began. This means this cluster of research is a relatively new hotspot. The research of this cluster showed a pattern similar to that of the previous group. In the early stage, researchers sequenced the changes of miRNA expression profile during osteogenic differentiation under different conditions, discovered several miRNAs with significant differences in expression levels, and used the database to predict possible targets (51,52). After that, the possible mechanism of miRNAs involved in osteogenic differentiation in different microenvironments was proposed successively. For example, miR-138 is related to the osteogenic differentiation of PDLSCs in the inflammatory microenvironment (53). The change of expression level of miR-214, miR-218, and others in the osteogenic differentiation of PDLSCs may be related to the Wnt pathway (54-56). Using miRNA to induce bone formation was a hot trend in this group of studies. Most of the current studies have focused on applying miRNA with therapeutic potential to bone tissue regeneration in the form of different carriers, especially to promote osseointegration after implant implantation (24,26,57,58). However, a miRNA is often expressed in various cells and has a wide range of targets in the interconnected regulatory network, which presents high requirements for the specificity of the miRNA drug delivery system (31).

Due to the limitation of time lag in co-citation analysis, there were only a small number of papers with high co-citation counts or high BC. Therefore, this cluster's bibliometric analysis may have missed some vital literature, which requires that researchers further read the original literature to uncover additional valuable research.

LncRNA/circRNA-miRNA-mRNA ceRNA network

The ceRNA hypothesis proposes a new mechanism of interaction between RNAs (59). Two main kinds of ceRNA, lncRNA, and circRNA, can compete with the miRNA response elements (MRE) on miRNA to act as a sponge for miRNA, inhibit the function of miRNA, and regulate gene expression. In periodontology and dental implantology, lncRNA (cluster 7, average year: 2012) focused on early research on this regulatory mechanism. Since 2014, the focus has gradually changed to circRNA (cluster 6, average year: 2017). Accerbi M introduced a set of isolation methods of total RNA in 2010 (60), which laid a good foundation for maximum recovery of high-quality RNA and subsequent RNA experimental analysis. In 2014, Guo developed a computational pipeline and applied it to the RNA sequence data set from the ENCODE project, eventually annotating more than 7,000 human circRNAs, greatly expanding the human understanding of circRNA (61). Gu's paper is an example of a study containing relatively high BC and co-citation counts in this emerging research hotspot so far. They performed a comprehensive analysis of lncRNA and circRNA in the process of osteogenic differentiation of PDLSCs and suggested that they may play a potential role as ceRNAs in promoting osteogenic differentiation and periodontal regeneration of PDLSCs (21).

Co-citation analysis was the most important method for determining the research hotspots and trends in this article. With the help of citation relationships, this method could reduce the influence of productive authors' research interest on the dataset to a certain extent. However, it is worth noting that this method could not distinguish the motives behind the authors' citations, which may not only be academic-related. For example, Cole observed that scientists are more likely to cite papers of friends and research colleges (62).

Burst keyword refers to a keyword that has a large frequency change in a short period. CiteSpace can clearly show the research frontier and trend of a certain field by detecting burst keywords from many literature keywords. For example, *microarray*, the earliest and longest burst keyword in this field, is one of the first tools for high-throughput analysis of a large number of miRNAs. Microarray is considered a reasonable choice when comparing the relative abundance of miRNAs related to a specific diagnosis (44). As mentioned above, Xie and other early researchers used microarray to locate several miRNAs with potential research value for subsequent researchers. In the last 5 years, more than half of the burst keywords have been related to bone tissue regeneration, suggesting that exploring the potential therapeutic value of miRNA has become a new hotspot in the current research. Wu recently constructed a miR-27a-enhanced drug delivery system to repair bone defects around the implant in a canine peri-implantitis model and to promote osseointegration and new bone formation (63).

We conducted a data visualization analysis of the research on miRNAs in periodontology and dental implantology for the first time. However, like other bibliometric analyses, this study still had some limitations: (I) Data source. In this study, only English literature records from Web of Science Core Collection were included. We cannot guarantee that all the relevant papers were retrieved. Researchers need to read the relevant literature more thoroughly to gain a deeper understanding of the research in this field. (II) Selection criteria. We choose different selection criteria for different node types. However, the actual literature records involved in the analysis were still determined by the threshold's size, which may have still missed some key papers that would have had a greater impact on the final results. It is necessary to compare and analyze the different nodes in the network diagram under different threshold settings. (III) Time lag. As mentioned above, some recently published high-quality studies may have been excluded because they had not yet received sufficient citations. When analyzing research hotspots and trends, we read the titles and abstracts of the last 3 years to eliminate this error as much as possible. (IV) Synonyms. We merged some synonyms and similar names according to the author affiliations, but we cannot guarantee that we eliminated the bias caused by synonyms and the same name (or the same abbreviation). (V) Lack of focus on the type of study. Researchers should be cautious when referring to this paper's conclusions because the hotspots/trends of specific study types (*in vivo* or *in vitro* experiments) may differ from the overall hotspots/trends in this field discussed in this paper.

Despite the above limitations, we still believe that our analysis reflected the research hotspots and trends of miRNA in periodontology and dental implantology to date. With the help of the data visualization software CiteSpace, we believe that our research will help future researchers quickly understand this field and choose the research direction they are interested in after further reading the relevant literature.

Conclusions

Since 2014, there has been a continuous increase in the number of papers on miRNA in periodontology and dental implantology. China and the United States have contributed the most research to this field. In previous studies, PDLSCs have been the most widely used materials, and the role of miRNA in the pathological process of periodontal disease and osteogenic differentiation have been the hotspots of research. Recent studies have shown that exploring the potential therapeutic ability of miRNAs to promote bone formation and bone regeneration, especially the promotion of osseointegration around implants, has become a new research hotspot. The ceRNA network is another recent research hotspot, and how it regulates miRNA at a deeper level in the above pathophysiological processes has gradually gained widespread attention. Thus, further research focuses on these topics may be more helpful to expedite the translation of miRNAs' basic scientific findings into new valuable diagnostic methods or biomaterials to bring a benefit to patients in the near future.

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Footnote

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