ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

# Biochemistry in Endodontics: A Bibliometric Analysis

## Endodontideki Biyokimya: Bir Bibliyometrik Analiz

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**ABSTRACT Objective:** The aim of the study is to perform a bibliometric analysis to evaluate the biochemical studies in endodontics. **Material and Methods:** The electronic search was performed in the Web of Science database with no time limit until 10 October 2023. All articles related to biochemistry in endodontics were included. The modularity Q index, the average silhouette, and the centrality values were determined. Publication growth trends, citations, keywords, countries, journals, and authors were analyzed using CiteSpace and VOSviewer. **Results:** A total of 831 (754 original articles and 77 reviews) studies were analyzed. The average growth rate between 1978 and 2023 has been approximately 10.13%. The first study was published in 1978, and 71 countries performed studies, however, the USA, Brazil, Japan, and China were the lead ones. A total of 3998 authors contributed to the publications. The Journal of Endodontics was the lead for the number of studies. **Conclusion:** The increasing publication trend indicates an increasing interest in biochemical studies in the endodontic literature. There was a global interest in biochemical studies in the endodontic literature. This bibliometric analysis presented a comprehensive glance at the biochemical studies in the endodontic field and reported the importance of biochemistry for the endodontic literature.

**Keywords:** Bibliometric analysis; endodontics; biochemistry; biomarker

**ÖZET Amaç:** Çalışmanın amacı, endodontideki biyokimyasal çalışmaları değerlendirmek için bibliyometrik analiz yapmaktır. **Gereç ve Yöntemler:** Elektronik arama, Web of Science veritabanında zaman sınırlaması olmadan 10 Ekim 2023 tarihine kadar gerçekleştirildi. Endodontideki biyokimya ile ilgili tüm makaleler dâhil edildi. Modülerlik Q indeksi, ortalama siluet ve merkezilik değerleri belirlendi. Yayın büyüme eğilimleri, alıntılar, anahtar kelimeler, ülkeler, dergiler ve yazarlar CiteSpace ve VOSviewer kullanılarak analiz edildi. **Bulgular:** Toplam 831 (754 orijinal makale ve 77 inceleme) çalışma analiz edildi. 1978-2023 yılları arasında ortalama büyüme oranı yaklaşık %10,13 olmuştur. İlk çalışma 1978 yılında yayınlanmıştır. Biyokimyasal konular 71 ülke tarafından çalışılmıştır ancak bunların başında ABD, Brezilya, Japonya ve Çin gelmektedir. Yayınlara toplam 3998 yazar katkıda bulunmuştur. Journal of Endodontics bu sayıdaki çalışmaların öncüsü oldu. **Sonuç:** Artan yayın eğilimi, endodonti literatüründe biyokimyasal çalışmalara olan ilginin arttığını göstermektedir. Biyokimyasal çalışmalara ilgi endodonti literatüründe küresel çapta gerçekleşmiştir. Bu bibliyometrik analiz endodonti alanındaki biyokimyasal çalışmalara kapsamlı bir bakış sundu. Bu çalışma endodonti literatürü için biyokimyanın önemini ortaya koymuştur.

**Anahtar Kelimeler:** Bibliyometrik analiz; endodonti; biyokimya; biyobelirteç

Endodontic infections are a common pathology in dental practice, they are controlled by immune system regulations and modulations, and their proper treatment is directly related to the long-term function of the tooth.[1-3] Pulpal and periapical tissue diseases affect various immune system cells and components.[2]

Endodontic infections are diagnosed clinically by a combination of objective and subjective tests.[3]

The severity and depth of endodontic infections guide the application of different treatment options such as vital pulp treatments and conventional endodontic treatment. However, clinical diagnostic tests cannot provide information about the depth and histologic status of the infection. In addition to this, the accuracy and validity of diagnostic tests are also questioned.[4-6]

Endodontic diseases result in the expression of numerous biomarkers in pulp blood, periapical tissue fluid, gingival crevicular fluid (GCF), granulation tissue, saliva, or systemic blood.[1,4] Biomarkers associated with the depth of the infection, symptoms, and irreversibility/reversibility is of diagnostic and prognostic importance. To analyze an endodontic infection via the increase of a biomarker in the GCF would be a valuable and non-invasive method. However, to establish this method in routine dental clinics, comprehensive research is needed for a specific, accurate, and reliable biomarker for each endodontic infection type.[5,6] A wide variety of biomarkers and infection types, the behavioral pattern of stem cells and the effects of growth factors were investigated with various study designs.[1,7-24] The dynamic effects of biochemical processes have been under the scope of endodontics for many years.

Bibliometric analysis, which provides properties of research including publication trends, and country or author data in a specific area, is a well-established method in science and is widely carried out in endodontics for different purposes. Bibliometric analysis was performed in endodontics for the top-cited articles in regenerative endodontics, top-downloaded articles, minimal invasive cavities, micro-computed tomography studies, trauma, and microcrack formation following endodontic procedures.[25-31] On the other hand, the effects of chemicals used in the various stages of endodontic treatment must be understood owing to the presence of surrounding vital tissues. That's why the scope of biochemical studies and bibliometric analysis also contains materialistic analysis.[27,32] This study aimed to evaluate the biochemical studies in endodontics. This analysis extensively utilized statistical, mathematical, and other techniques to determine the distribution of research achievements, subject development, and research trends within a particular field.

## ▌MATERIAL AND METHODS

### DATA AND RESEARCH METHODS

This study was performed in accordance with the Helsinki Declaration and ethical consent was not applicable. Web of Science Core Collection (WOS),

one of the important research databases, was preferred for the data of this study. In this study, data were downloaded from the Web of Science Core Collection on 10.10.2023, and certain keywords were determined to access publications on the connection between endodontics and biomarkers. The search code used was Topic=("endodontic* treatment" OR endodontic* OR "root canal treatment" OR "root canal therapy" OR "regenerative endodontic*" OR "pulp revascularization" OR "pulp revitalization" OR "reversible pulpitis" OR "irreversible pulpitis" OR "dental pulp diseases" OR "pulp tissue" OR "pulp blood" OR "inflammatory pulp disease" OR "apical periodontitis" OR "periapical periodontitis" OR "periapical abscess") AND Topic=(molecular OR molecules OR biomarker* OR "biological marker*" OR cytokine OR "inflammatory cytokine" OR "molecular mediator*" OR "growth factor*" OR biochemistry OR biochemical). For the database created with the specified keywords, the document type was chosen as articles and reviews, and the literary language was English. Therefore, meeting abstracts, proceeding papers, corrections, editorial material, and book chapters are excluded (Figure 1). After the determined criteria, 1786 studies were reached. Two researchers independently scanned and examined the determined documents, and in case of disagreement, a third independent researcher's opinion was obtained. Studies that were determined to be unrelated to the research topic were removed.

Finally, 831 academic studies were recorded for analysis with their bibliometric data. In the study, 77 of these are review articles and the rest are original research articles. No time limit is specified to observe the entire development and evolution of the research field from its birth. All data were obtained through the public database and had nothing to do with any human subject.

In this study, bibliometric analysis and descriptive statistics were applied to analyze and visualize biomarkers in endodontic in the following aspects: (1) the fundamental characteristics of the biomarkers in endodontic publications growth trend, (2) the interactions between hot topics, and the co-document citation and keywords (3) the most influential countries/regions, journals, and authors. In this study, bib-
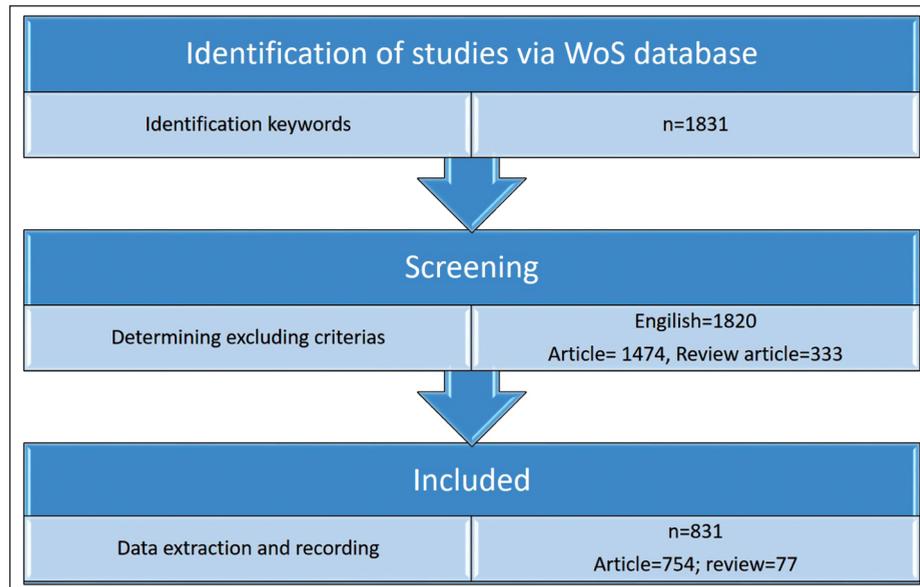
**FIGURE 1:** Flow chart of research and analysis of endodontics and biomarkers research.

liometric analysis was conducted using CiteSpace (Drexel University, Philadelphia, PA, USA) and VOSviewer (Leiden University, Leiden, Netherlands) analysis software. Descriptive statistics were performed using Excel (Microsoft Corporation, Redmond, WA, USA) and SPSS (IBM, Endicott, NY, USA). The software versions utilized for the analysis in this study were as follows: CiteSpace (6.2.R4) Advanced (updated on June 30, 2023, software available at gingival crevicular fluid and VOSviewer version 1.6.19.

CiteSpace, by analyzing both the content of publications and citation networks, provides insights into the structure and dynamics of specific research fields or areas. The visual maps generated by CiteSpace for bibliometric analysis consist of nodes and links, where nodes are used to represent analytical entities such as authors, journals, references, and keywords. Node size reflects the total co-occurrence frequency of an item, while node thickness and ring color indicate the time periods of co-occurrence for that item. It was employed three distinct structural metrics to assess the structural integrity of the generated networks. First, the modularity Q index was utilized to determine the degree to which the network can be subdivided into smaller components. Second, the av-

erage silhouette score was employed to evaluate the quality and uniformity of the clusters formed within the network. Finally, centrality values were measured as a metric to assess the ability of nodes to effectively connect with other nodes in the network.

In addition to these structural metrics, temporal metrics were also considered in the node analysis. One noteworthy metric is citation bursts, which serve as important indicators of research impact. Burst detection is a commonly adopted computational method for elucidating abrupt shifts in events. A citation burst identifies keywords, authors, institutions, or documents that exhibit substantial changes in the literature over time. Finally, the timeline view offers an overview of how the cluster has evolved over time, shedding light on whether any trends have persisted throughout the years.

VOSviewer visually presents the node network graphically by utilizing two standardized measures: the number of connections and the overall strength of these connections. The size of nodes and the internal lines that link them reflect the scale and robustness of these connections. Co-citation analysis and clustering were performed to unveil the intellectual structure, while keyword analyses were conducted to identify potential future themes.

## RESULTS

### GROWTH TREND

For the study, no time limit has been imposed in order to see all the development and change of this field from past to present. The analysis contained all WOS studies that recorded all data up to date. The distribution chart of the number of publications by year was created (Figure 2). The increasing trend in the number of publications shows that the field is developing. Thus, with this study, a portrait of the last 46 years (1978-2023) in the field was revealed.

The first study was published in 1978.[32] The graphic can be divided into two periods, while the first period was a stagnant period of approximately 20 years between 1978 and 1997, the period after 1998, when developments in the field were observed, can be mentioned. Over the past 45 years, the annual average growth rate of publications related to biomarkers in endodontics has been approximately 10.13%. Since 2023 has not yet been completed during the preparation of the manuscript of this study, it is not included in the growth rate calculation.

### CONTRIBUTION OF COUNTRIES/REGIONS

To gain a deeper understanding of countries and regions with significant broadcasting activity, we imported 831 data into CiteSpace. In total, 71 countries or regions have contributed research papers in this field. Collaborative relationships highlight the robust connections between these countries and regions. Figure 3 clearly shows that the top 11 countries/regions in terms of number of publications is Brazil (Counts: 166; 19.98%), USA (counts: 160; 19.25%), and P.R. China (counts: 146; 17.57%). The USA is the country that conducts the oldest and most well-established research in this field. In addition, the USA, with the highest centrality value of 0.45, is the key country that cooperates with other countries. The USA, Brazil, and Japan are the countries with high centrality values, respectively. Purple rings around the three nodes represent countries with high centrality values. The citation burst represents the countries that have received citations faster than expected in a
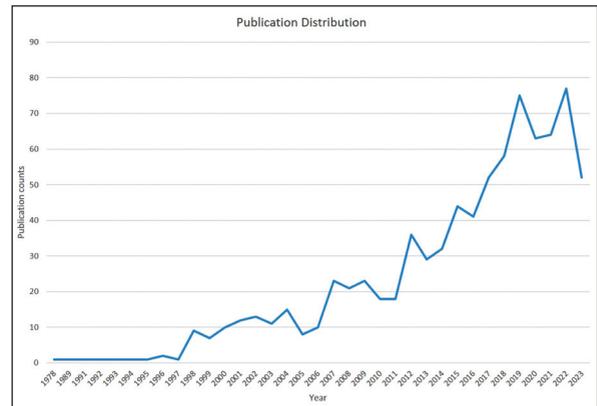


**FIGURE 2:** Distribution of annual publications of biomarkers in endodontic research.
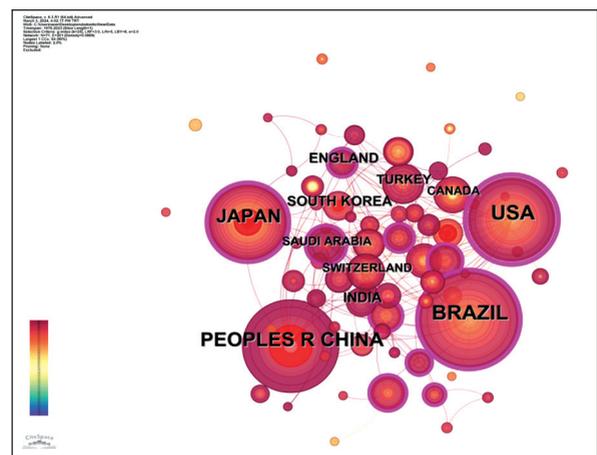


**FIGURE 3:** Map of the countries' collaboration network. Purple circles show nodes with centrality values greater than 0.1, while red nodes represent citation bursts.

short time. A total of five countries out of 71 countries had a citation burst (Table 1). China has recently done remarkable work in this field in recent years.

### THE MOST INFLUENTIAL JOURNAL

In the scope of biochemical endodontics, 831 publications were published in a total of 245 different journals. The threshold value for journal analysis determined by at least five publications and at least one citation is 20 (Figure 4A). A set of 3607 cited sources cited by 831 publications was obtained. Figure 4B shows the Cited source with a threshold value of 104 for sources with at least 50 citations. The top ten most productive and journals were demonstrated in Table 2.

| TABLE 1: Top 5 countries with the strongest citation bursts. | | | | | |
|---|---|---|---|---|---|
| Countries | Year | Strength | Begin | End | 1978-2023 |
| USA | 1978 | 5.67 | **1991** | 2003 | |
| Japan | 1996 | 12.44 | **1996** | 2011 | |
| Finland | 2000 | 4.81 | **2000** | 2010 | |
| South Korea | 2000 | 4.77 | **2012** | 2016 | |
| China | 2006 | 4.29 | **2018** | 2019 | |
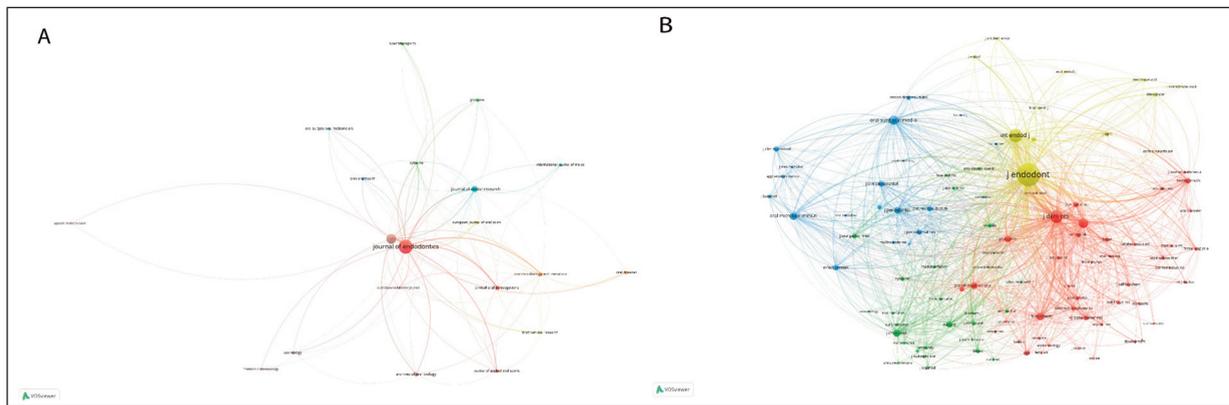


**FIGURE 4:** Visual map of the most influential journals **(A)** Visual map of productive journals with VOSviewer **(B)** Visual map of the cited journal with VOSviewer.

| TABLE 2: Top 10 most productive journal and co-cited cited journal. | | | | | |
|---|---|---|---|---|---|
| | **Productive journal** | | | **Cited journal** | |
| **Rank** | **Journal name** | **Counts** | **Citations** | **Cited journal name** | **Citations** |
| 1 | Journal of Endodontics | 203 | 5,859 | Journal of Endodontics | 4,994 |
| 2 | International Endodontic Journal | 98 | 1,938 | International Endodontic Journal | 1,646 |
| 3 | Journal of Dental Research | 36 | 1,672 | Journal of Dental Research | 1,466 |
| 4 | Archives of Oral Biology | 18 | 278 | Archives of Oral Biology | 877 |
| 5 | Clinical oral Investigations | 17 | 238 | Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology | 781 |
| 6 | Oral Microbiology and Immunology | 13 | 713 | Oral Microbiology and Immunology | 534 |
| 7 | Oral Diseases | 13 | 299 | Journal of Biological Chemistry | 532 |
| 8 | Journal of Applied Oral Science | 11 | 149 | Journal of Immunology | 476 |
| 9 | European Journal Of Oral Science | 10 | 360 | Proceedings of the National Academy of Sciences USA | 447 |
| 10 | PloS One | 10 | 346 | Journal of Periodontology | 409 |

## ANALYSIS OF THE CO-AUTHORSHIP AND THE MOST INFLUENTIAL AUTHORS

Table 3 shows the top ten active authors and the ten most cited influential authors in this literature. A total of 3998 different authors participated in the publication of the literature on biomarkers in endodontics, with an average of 4.8 or approximately five authors per document. 831 publications were published in a total of 3998 different authors. The threshold value for author analysis determined by at least five publi-cations and at least one citation is 46 (Figure 5A). A total of 19068 different authors have been cited in the field, with 30 authors receiving more than 50 citations (Figure 5B). In other words, 30 authors have been cited more than 50 times. In general, the analysis emphasizes the importance of the authors' research in enhancing our comprehension of the interactions biochemistry in endodontics. Each of them has made distinctive contributions to the progression of knowledge in this field.

**TABLE 3:** Most prolific & most cited authors.

| | Most prolific authors | | | Most cited authors | |
|---|---|---|---|---|---|
| Rank | Author | Document counts | Citations | Author | Citations |
| 1 | Gomes, Brenda p.f.a. | 13 | 343 | Squeira, J F | 340 |
| 2 | Squeira, J F | 12 | 900 | Nair, PNR | 146 |
| 3 | Letra, Ariadne | 11 | 422 | Stashenko, P | 146 |
| 4 | Cooper, Paul R | 11 | 279 | Galler, KM | 121 |
| 5 | Garlet, Gustovo Pompermaier | 10 | 402 | Nakashima, M | 114 |
| 6 | Roças, Isabela N. | 10 | 739 | Huang, GTJ | 109 |
| 7 | Okiji, Takashi | 9 | 89 | Gronthos, S | 109 |
| 8 | Armada, Luciana | 9 | 71 | Gomes, Brenda p.f.a | 108 |
| 9 | Neves de Brito, L.C | 8 | 165 | Kawashima, N | 99 |
| 10 | Vieira, Ieda quercia | 8 | 165 | Roças, Isabela N | 98 |
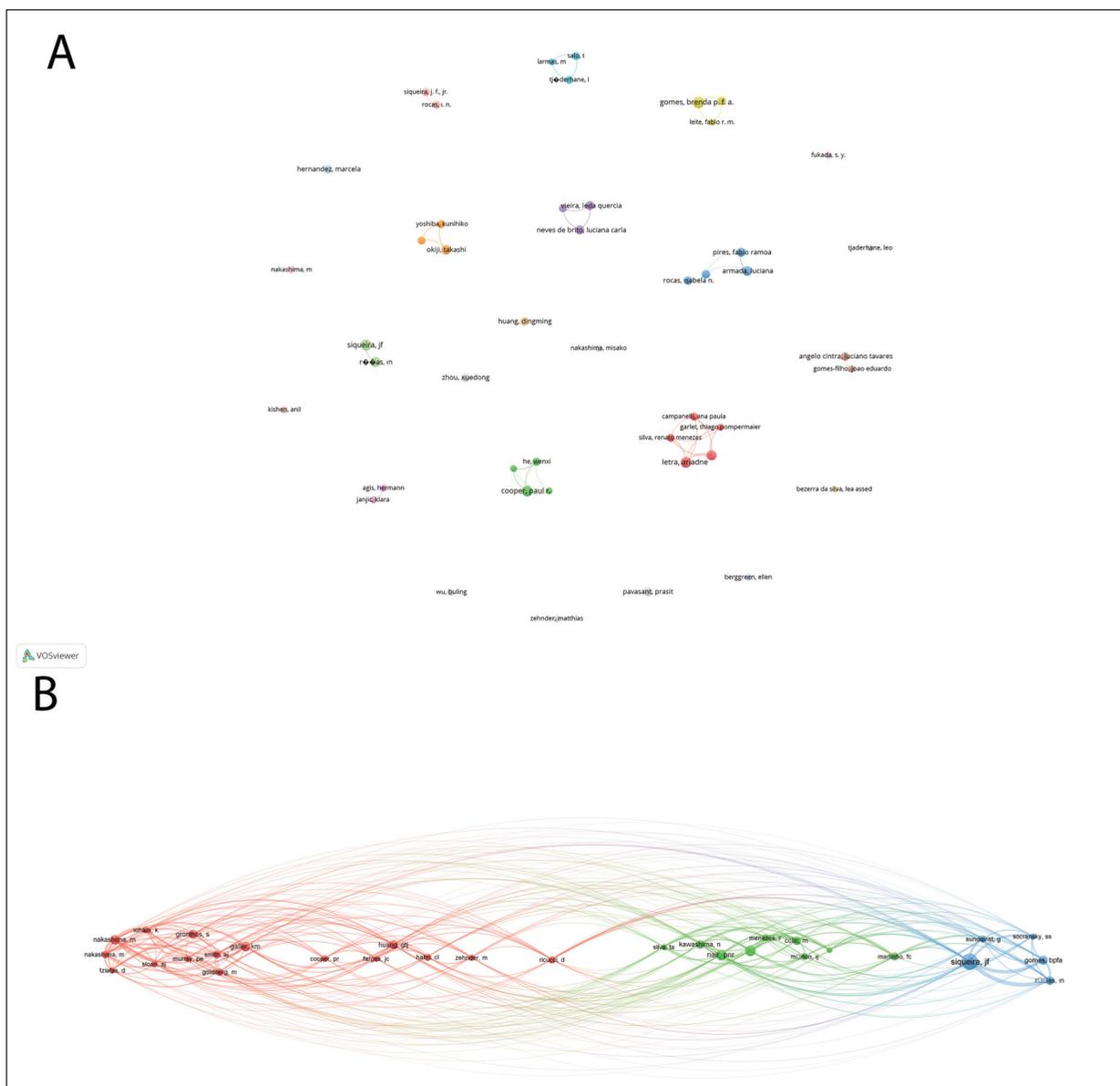


**FIGURE 5: (A)** Prolific authors network **(B)** Network map of cited authors.

## RESEARCH HOTSPOTS: CO-WORD ANALYSIS AND CLUSTERING ANALYSIS OF KEYWORDS

Keywords were taken from 831 publications and constitute a significant part of the research. Keyword co-occurrence analysis provides a reasonable definition of research hotspots, and the resulting keywords can represent research fronts within a certain period of time.[33] The co-occurrence of two keywords in an article results in keyword co-occurrence, indicating a relationship between the two concepts. Keyword analysis was performed using VOSviewer to discover the most common themes related to biomarkers in endodontic research. A total of 1,860 keywords were identified in 831 documents. Table 4 presents the most important keywords used in biochemical endodontic research. The frequency of occurrence of these keywords over nearly 50 years demonstrates their importance and relevance in shaping research on biomarkers in endodontics (Figure 6). Co-word (keyword co-occurrence) network visualization using

| TABLE 4: Top 20 keywords. | | | |
|---|---|---|---|
| Keyword | Frequency | Keyword | Frequency |
| Apical periodontitis | 96 | Regeneration | 20 |
| Dental pulp | 79 | Periapical lesions | 19 |
| Inflammation | 68 | inflammation | 18 |
| Endodontics | 52 | Vascular Endothelial Growth Factor | 16 |
| Cytokines | 52 | Bacteria | 16 |
| Regenerative endodontics | 34 | İmmunohistochemistry | 16 |
| Pulpitis | 31 | Growth factors | 15 |
| Angiogenesis | 25 | Periapical periodontitis | 15 |
| Cytokine | 25 | Periapical lesion | 15 |
| Dental Pulp Stem Cell | 22 | Enterecoccus feacalis | 15 |
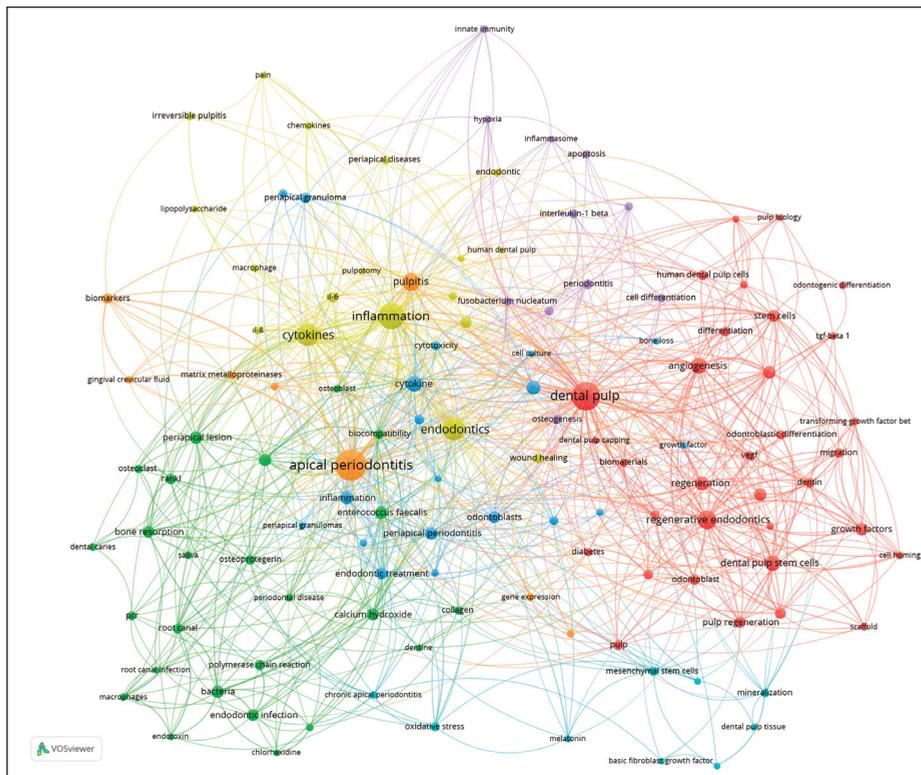


**FIGURE 6:** Co-word (keyword co-occurrence) network visualization.

VOSviewer. Each node means a keyword in the network and each color represents a thematic cluster. The size of the node represents the frequency of the keyword. The connections between nodes in the network mean the co-occurrence of keywords. The thickness of the connections means the strength of the co-occurrence of keywords. The larger the node indicates the more frequently the keyword appears.

Citation burst refers to the sudden frequent occurrence of a keyword within a certain period of time. According to the detection of words that emerge with high frequency and rapid growth rate within a certain period of time, keywords with high burst density are an important indicator that reflects the research hot spots, boundaries, and the latest trends. In total, 15 keywords had a citation burst (Table 4 and Table 5). The keywords in the box are keywords that have come to the fore in recent years. Co-occurring keywords can provide insight into recent trends and possibly future research directions.

Figure 7 presents a keyword clustering visualization that was created through visual mapping of keyword co-occurrence and clustering labels determined using the Log-Likelihood Ratio. Clustering analysis was performed based on the similarity of keywords. The results showed that current research on biomarkers in endodontic research mainly focuses on five topics (If the number of cluster elements is less than ten, the program automatically shows the cluster in gray).

Clusters are numbered starting from zero, and the size of the clusters decreases as the number increases.[20] CiteSpace evaluates the clustering effect with two metrics, modularity (Q) and Silhouette (S). Q is an evaluation index of network modularity and a higher Q value means that the network is better clustered. Q takes the range [0, 1] and Q>0.3 means that the network structure is important. S is the index used to measure the homogeneity of the network. The closer it is to one, the higher the homogeneity of the network. When S is 0.7, the clustering result has high reliability. If the value is above 0.5, the clustering result can be considered reasonable. As can be seen from the figure, Q=0.4107 and S=0.7824, we can say that the clustering structure can be considered reliable.

## DOCUMENT CO-CITATION ANALYSIS

Document co-citation analysis (DCA) is a type of frequency-based analysis where two documents are cited together. CiteSpace performs such analyses both by considering documents downloaded from scientific databases and by examining references in texts. Co-citation analysis is frequently used in the field of bibliometrics to examine the development of scientific fields, identify influential studies, and track

| TABLE 5: Top 15 keywords with the strongest citation bursts. | | | | | |
|---|---|---|---|---|---|
| **Keywords** | **Year** | **Strength** | **Begin** | **End** | **1991-2023** |
| Cells | 1998 | 14.98 | 1998 | 2012 | |
| Identification | 2002 | 6.24 | 2002 | 2012 | |
| Polymerase chain reaction | 2002 | 3.86 | 2002 | 2007 | |
| Induction | 2004 | 5.25 | 2004 | 2007 | |
| Apical periodontitis | 2007 | 11.33 | 2008 | 2014 | |
| Expression | 1998 | 6.37 | 2008 | 2013 | |
| Necrosis factor alpha | 2013 | 5.67 | 2013 | 2017 | |
| Gene expression | 2015 | 5.92 | 2015 | 2018 | |
| Mesenchymal stem cells | 2015 | 5.11 | 2015 | 2017 | |
| Lesions | 2015 | 5.03 | 2015 | 2018 | |
| Endothelial growth factor | 2017 | 5.34 | 2017 | 2018 | |
| Calcium hydroxide | 2017 | 4.56 | 2017 | 2020 | |
| Porphyromonas gingivalis | 2018 | 3.73 | 2018 | 2019 | |
| Mechanisms | 2019 | 6.46 | 2019 | 2020 | |
| Regenerative endodontics | 2016 | 6.32 | 2020 | 2023 | |
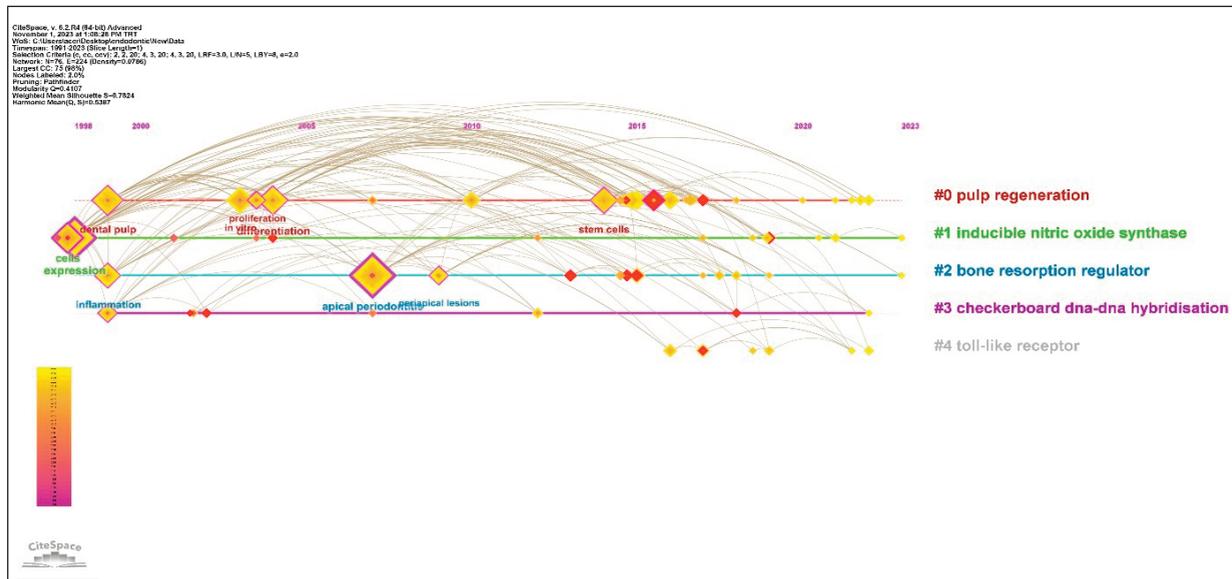
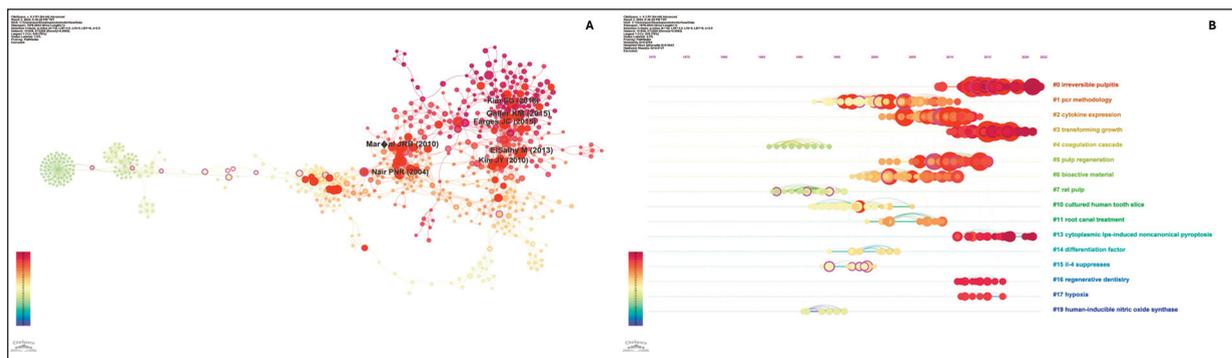**FIGURE 7:** The keyword clustering timeline visualization.



**FIGURE 8:** DCA network image **(A)** Timeline map of DCA clusters **(B)** (Clusters represent the topics of the cited reference).
DCA: Document co-citation analysis.

the evolution of research topics over time. The total number of different valid references in 831 publications on biomarkers in endodontics is 25,569. The average number of references per publication is approximately 30.77.

Network images of 25,569 different references from a total of 831 publications were created with CiteSpace. The network consists of 838 nodes and 2,272 links (Figure 8A). A citation burst can be interpreted as intense interest from the research community in the underlying work, and if a cluster contains a large number of publications with strong citation bursts, then the cluster as a whole is considered to encompass an active area of research; an

emerging trend. The clusters we obtained for DCA showed a modularity Q index of 0.8766 and an average silhouette value of 0.9538. The nodes thus form a network that can be partitioned into clusters, each of which is highly homogeneous. As the main clusters identified in DCA, they are highly homogeneous. Clusters 0.3 and 13 are active reference subjects (Figure 8B).

## DISCUSSION

This is the first bibliometric analysis in the field of the biochemical perspectives of endodontics. Bibliometric analysis is a popular method that exhibits the tendency of different subfields.[29-31,33,34] Besides, the

deficiencies in the endodontic literature may be mapped.[30,31] This study emphasis on the evolution of hotspots, publication trends, citation structures, prolific authors, institutional affiliations, and countries. By analyzing publication volume and citation metrics, researchers may better understand the impact and importance of biochemistry.

Biochemical studies in the endodontic literature began in 1,978 with the evaluation of the effect of a chemical on pulp tissue.[32] It continued in a more stagnant form until approximately the 2000s. Since the early 2000s, biochemical studies have begun to increase, reaching their peak, especially in 2019 and 2022. There was a sharp increase between 2016 and 2019. This can be explained by the investigations of stem cell development and proliferation and effective signaling pathways, or potential biomarkers in medicine may have reflections in the endodontic literature.

This increase has developed over the years in direct proportion to the development of biochemical methods and technologies that enable the detection of biomarkers from saliva, GCF, and pulp blood or tissue.[1,4] Advances in biomarker detection techniques have a great potential to revolutionize endodontic diagnosis and treatment.[7] These advances led to earlier and more accurate detection of endodontic biomarkers and also allowed rapid and targeted treatment searching.[4] These advances accelerated the biochemical studies that query the non-invasive methods for a more accurate diagnosis.[4-7] Endodontic treatment based on biomarker profiles is an exciting area of future research. By analyzing an individual's unique biomarker profile, clinicians can tailor treatment plans to the patient's specific needs and characteristics. Additionally, biomarker profiles can be used to monitor treatment progress and predict long-term outcomes.[6,8]

Studies on biochemical studies in endodontics have focused on identifying and understanding specific biomarkers that may aid in the diagnosis, prognosis, and treatment of endodontic diseases.[4-9] The increasing number of biochemical studies in endodontic literature on a yearly basis can also be explained by the evaluation of the validity of new biomarkers discovered and studied in medicine.

On the other hand, there was a decrease/stagnation in publication distribution in 2020 and 2021. This situation can be explained by the deceleration in studies that require obtaining samples from patients due to the coronavirus disease-2019 (COVID-19) pandemic that has affected the whole world. In addition, it can be concluded that other *in vitro* biochemical study types have slowed down due to the general online work periods during the COVID-19 pandemic.

When the results were analyzed in terms of distribution in the world, it was seen that biochemical studies are examined on a wide scale in 71 countries. Biochemical studies were carried out mostly in the USA, Brazil, and China. The broad spectrum of these studies can be attributed to the fact that academician endodontists in the world tend to reduce gray areas in clinical practices and are in search of more objective diagnostic tools. With these studies, by analyzing these biomarkers, clinicians can potentially detect irreversible pulpitis at an early stage, even before clinical symptoms appear.[4,6] This early diagnosis is crucial for timely, accurate, and effective treatment. Biomarkers may be helpful in assessing the severity and prognosis of pulp and periapical diseases.[8,9-11] The presence and levels of certain biomarkers can provide information about the likelihood of success in root canal therapy or the need for tooth extraction. Biomarker data can guide clinicians in making informed decisions about the most appropriate treatment approach for a particular case.[12] For example, changes in specific biomarker levels can indicate whether inflammation has resolved after endodontic treatment or whether further intervention is required.

For the author parameter, it is seen that approximately 400 different authors participated in biochemical studies. This shows that biochemical studies in endodontics are interested in a wide range of authors rather than a core team. This shows that biochemical studies in endodontics are interested in a wide range of authors rather than a core team. In addition, the high citation scores in the studies indicate that biochemical studies serve as a crossroads to other fields and attract the attention of endodontic academics. In particular, according to our results, the USA, Japan, Finland, South Korea, and China were observed as countries with citation bursts. In terms

of journals, according to our results, two journals that biochemical studies are most cited; the "Journal of Endodontics" and the "International Endodontic Journal". These two journals stand out as the journals that devote the most space to studies evaluating the endodontic literature from a biochemical perspective.

When the keywords of biochemical studies are examined, it was seen that the most prominent terms are "apical periodontitis", "dental pulp", "inflammation", "endodontics", "cytokines", "regenerative endodontics", and "pulpitis". This table emphasizes the need for the presence of biomarkers in the diagnosis, treatment, and prognosis of endodontic inflammatory diseases. In this context, cytokines, which are biomarkers that are expressed in inflammatory diseases, were specifically examined. The pursuit in the literature for non-invasive diagnosis of diseases by up-regulating or down-regulating potential cytokines in biofluids such as saliva or GRF has been clearly demonstrated by our study. On the other hand, it can be seen that regenerative endodontics has also found wide coverage in biochemical studies in the literature. The detection of biochemical molecules and signaling pathways that are active in the differentiation and proliferation of stem cells during regeneration constitutes the basis of clinical treatment procedures.

In our study, electronic research was performed in the WOS database that has many advantages compared to others. It is a reputable and comprehensive bibliographic database that provides extensive access to peer-reviewed journal publications, bibliographic information, and citations.[26,31,33] However, further studies that are performed in various databases are needed.

In conclusion, biochemical studies contribute to the scientific understanding of the pathophysiology of endodontic diseases and materials. This research may lead to the development of new diagnostic tools, materials, and treatment strategies. Understanding the molecular mechanisms underlying endodontic diseases or the effects of the chemical materials may also lead to the development of targeted therapies that may improve treatment outcomes and patient comfort. These studies provide valuable information for both clinicians and researchers, allowing for more precise and personalized patient care in endodontics.

## CONCLUSION

Within the limitation of the study, it was concluded that the biochemical studies have an increasing impact on the endodontic literature. According to this analysis, this increasing interest was valid globally such that 71 countries reported biochemical studies, and approximately 4000 authors studied these topics. This bibliometric analysis clearly exhibited the growing tendency for endodontic biochemistry.

### *Conflict of Interest*

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

### *Authorship Contributions*

***Idea/Concept:*** *Zerrin Barut, Deniz Yanık;* ***Design:*** *Zerrin Barut, Deniz Yanık;* ***Control/Supervision:*** *Zerrin Barut, Deniz Yanık;* ***Data Collection and/or Processing:*** *Zerrin Barut, Deniz Yanık;* ***Analysis and/or Interpretation:*** *Zerrin Barut, Deniz Yanık;* ***Literature Review:*** *Zerrin Barut, Deniz Yanık;* ***Writing the Article:*** ***Critical Review:*** *Zerrin Barut, Deniz Yanık;* ***References and Fundings:*** *Zerrin Barut;* ***Materials:*** *Zerrin Barut, Deniz Yanık.*

# REFERENCES

1. Brizuela C, Meza G, Mercadé M, Inostroza C, Chaparro A, Bravo I, et al. Inflammatory biomarkers in dentinal fluid as an approach to molecular diagnostics in pulpitis. Int Endod J. 2020;53(9):1181-91. [Crossref] [PubMed]

2. Donnermeyer D, Dammaschke T, Lipski M, Schäfer E. Effectiveness of diagnosing pulpitis: a systematic review. Int Endod J. 2023;56 Suppl 3:296-325. [Crossref] [PubMed]

3. Džopalić T, Tomić S, Bekić M, Vučević D, Mihajlović D, Eraković M, et al. Ex vivo study of IL-6 expression and function in immune cell subsets from human periapical lesions. Int Endod J. 2022;55(5):480-94. [Crossref] [PubMed]

4. Karrar RN, Cushley S, Duncan HF, Lundy FT, Abushouk SA, Clarke M, El-Karim IA. Molecular biomarkers for objective assessment of symptomatic pulpitis: a systematic review and meta-analysis. Int Endod J. 2023;56(10):1160-77. [Crossref] [PubMed]

5. Edwards D, Bailey O, Stone SJ, Duncan H. How is carious pulp exposure and symptomatic irreversible pulpitis managed in UK primary dental care? Int Endod J. 2021;54(12):2256-75. [Crossref] [PubMed]

6. Duncan HF, Cooper PR, Smith AJ. Dissecting dentine-pulp injury and wound healing responses: consequences for regenerative endodontics. Int Endod J. 2019;52(3):261-6. [Crossref] [PubMed]

7. Al Natour B, Lundy FT, About I, Jeanneau C, Dombrowski Y, El Karim IA. Regulation of caries-induced pulp inflammation by NLRP3 inflammasome: a laboratory-based investigation. Int Endod J. 2023;56(2):193-202. [Crossref] [PubMed] [PMC]

8. Bakhsh A, Moyes D, Proctor G, Mannocci F, Niazi SA. The impact of apical periodontitis, non-surgical root canal retreatment and periapical surgery on serum inflammatory biomarkers. Int Endod J. 2022;55(9):923-37. [Crossref] [PubMed] [PMC]

9. Braz-Silva PH, Bergamini ML, Mardegan AP, De Rosa CS, Hasseus B, Jonasson P. Inflammatory profile of chronic apical periodontitis: a literature review. Acta Odontol Scand. 2019;77(3):173-80. [Crossref] [PubMed]

10. Rechenberg DK, Galicia JC, Peters OA. Biological markers for pulpal inflammation: a systematic review. PLoS One. 2016;11(11):e0167289. [Crossref] [PubMed] [PMC]

11. Araujo-Pires AC, Francisconi CF, Biguetti CC, Cavalla F, Aranha AM, Letra A, et al. Simultaneous analysis of T helper subsets (Th1, Th2, Th9, Th17, Th22, Tfh, Tr1 and Tregs) markers expression in periapical lesions reveals multiple cytokine clusters accountable for lesions activity and inactivity status. J Appl Oral Sci. 2014;22(4):336-46. [Crossref] [PubMed] [PMC]

12. Elsalhy M, Azizieh F, Raghupathy R. Cytokines as diagnostic markers of pulpal inflammation. Int Endod J. 2013;46(6):573-80. [Crossref] [PubMed]

13. Lee H, Bae A, Kim J, Kingsley K. differential effects of extracellular matrix glycoproteins fibronectin and laminin-5 on dental pulp stem cell phenotypes and responsiveness. J Funct Biomater. 2023;14(2):91. [Crossref] [PubMed] [PMC]

14. Loureiro C, Buzalaf MAR, Moraes FRN, Ventura TMO, Pelá VT, Pessan JP, Jacinto RC. Quantitative proteomic analysis in symptomatic and asymptomatic apical periodontitis. Int Endod J. 2021;54(6):834-47. [Crossref] [PubMed]

15. Montis N, Cotti E, Noto A, Fattuoni C, Barberini L. Salivary metabolomics fingerprint of chronic apical abscess with sinus tract: a pilot study. ScientificWorldJournal. 2019;2019:3162063. [Crossref] [PubMed] [PMC]

16. Naruse H, Itoh S, Itoh Y, Kagioka T, Abe M, Hayashi M. The Wnt/β-catenin signaling pathway has a healing ability for periapical periodontitis. Sci Rep. 2021;11(1):19673. [Crossref] [PubMed] [PMC]

17. Sakagami H, Nakatani S, Enomoto A, Ota S, Kaneko M, Sugimoto M, et al. Multi-omics analysis of anti-inflammatory action of alkaline extract of the leaves of Sasa sp. J Clin Med. 2021;10(10):2100. [Crossref] [PubMed] [PMC]

18. Sharma R, Kumar V, Logani A, Chawla A, Mir RA, Sharma S, et al. Association between concentration of active MMP-9 in pulpal blood and pulpotomy outcome in permanent mature teeth with irreversible pulpitis - a preliminary study. Int Endod J. 2021;54(4):479-89. [Crossref] [PubMed]

19. Sirin DA, Ozcelik F, Ersahan S, Pence HH. The importance of inflammatory biomarkers, IL-6 and PAPP-A, in the evaluation of asymptomatic apical periodontitis. Odontology. 2021;109(1):250-8. [Crossref] [PubMed]

20. Wei XL, Luo L, Chen MZ, Zhou J, Lan BY, Ma XM, et al. Temporospatial expression of neuropeptide substance P in dental pulp stem cells during odontoblastic differentiation in vitro and reparative dentinogenesis in vivo. J Endod. 2023;49(3):276-85. [Crossref] [PubMed]

21. Cai X, Gong P, Huang Y, Lin Y. Notch signalling pathway in tooth development and adult dental cells. Cell Prolif. 2011;44(6):495-507. [Crossref] [PubMed] [PMC]

22. Cordeiro MM, Dong Z, Kaneko T, Zhang Z, Miyazawa M, Shi S, et al. Dental pulp tissue engineering with stem cells from exfoliated deciduous teeth. J Endod. 2008;34(8):962-9. [Crossref] [PubMed]

23. Paino F, La Noce M, Giuliani A, De Rosa A, Mazzoni S, Laino L, et al. Human DPSCs fabricate vascularized woven bone tissue: a new tool in bone tissue engineering. Clin Sci (Lond). 2017;131(8):699-713. [Crossref] [PubMed] [PMC]

24. Rezai Rad M, Hosseinpour S, Ye Q, Yao S. Dental Tissues originated stem cells for tissue regeneration. In: Moharamzadeh K, Walsh LJ, Hosseinpour S, eds. Regenerative Approaches in Dentistry: An Evidence-Based Perspective. 1st ed. Springer International Publishing; 2021. p.9-33. [Crossref]

25. Adnan S, Ullah R. Top-cited articles in regenerative endodontics: a bibliometric analysis. J Endod. 2018;44(11):1650-64. [Crossref] [PubMed]

26. Shamszadeh S, Asgary S, Nosrat A. Regenerative endodontics: a scientometric and bibliometric analysis. J Endod. 2019;45(3):272-80. [Crossref] [PubMed]

27. Ahmad P, Elgamal HAM. Citation classics in the journal of endodontics and a comparative bibliometric analysis with the most downloaded articles in 2017 and 2018. J Endod. 2020;46(8):1042-51. [Crossref] [PubMed]

28. Silva EJNL, Pinto KP, Ajuz NC, Sassone LM. Ten years of minimally invasive access cavities in endodontics: a bibliometric analysis of the 25 most-cited studies. Restor Dent Endod. 2021;46(3):e42. [Crossref] [PubMed] [PMC]

29. Aksoy U, Küçük M, Versiani MA, Orhan K. Publication trends in micro-CT endodontic research: a bibliometric analysis over a 25-year period. Int Endod J. 2021;54(3):343-53. [Crossref] [PubMed]

30. Ahmad P, Vincent Abbott P, Khursheed Alam M, Ahmed Asif J. A bibliometric analysis of the top 50 most cited articles published in the Dental Traumatology. Dent Traumatol. 2020;36(2):89-99. [Crossref] [PubMed]

31. Tonelli SQ, de Toubes KS, Brabo Pereira AM, de Oliveira Miranda AC, Fernandes LL, Nunes E, et al. Dentinal microcracks induced by endodontic procedures: a scientometric and bibliometric analysis. J Conserv Dent. 2022;25(1):78-87. [Crossref] [PubMed] [PMC]

32. Lazzari EP, Ranly DM, Walker WA. Biochemical effects of formocresol on bovine pulp tissue. Oral Surg Oral Med Oral Pathol. 1978;45(5):796-802. [Crossref] [PubMed]

33. Xu Z, Zhu Y, Hu Y, Huang M, Xu F, Wang J. Bibliometric and visualized analysis of neuropathic pain using Web of Science and CiteSpace for the past 20 years. World Neurosurg. 2022;162:e21-e34. [Crossref] [PubMed]

34. Ma W, Yang YB, Xie TT, Xu Y, Liu N, Mo XN. Cerebral small vessel disease: a bibliometric analysis. J Mol Neurosci. 2022;72(11):2345-59. [Crossref] [PubMed] [PMC]