

## RESEARCH ARTICLE

# Application of Calcium Phosphate as Remineralizing Agent in Oral Healthcare: A Bibliometric and Scientometric Analysis

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## Abstract:

There has been increased interest in developing bioactive agents based on calcium phosphate (CaP) in oral care for enhancing enamel and dentin remineralization. This bibliometric and scientometric analysis explores the interdisciplinary view of calcium phosphates-based for alternative oral care concepts in preventive dentistry. Bibliometric analyses were performed using VOSviewer software taking SCOPUS as the main database for literatures retrieval. The analysis revealed highest number of CaP-related articles were published within 10 years that provide insights into the past and recent trends in the applications of CaP in oral care. Further, top three countries with the highest number of publications includes, the United States (n=58), China (n=50) and India (n=23). Finally, present study provides data on literatures, countries and authors that have been involved in CaP research extensively for the past years. Also, this study will help researchers, academicians and students to find suitable article for their referral in terms of the use of CaP as a biomaterial in dentistry.

**Keywords:** bibliometric, calcium phosphate, scientometric, tooth remineralization

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## 1. INTRODUCTION

Dental caries or tooth decay is a highly prevalence oral infectious disease. Increased caries incidence has been one of the most common health problems and economic burdens globally (Bowen et al., 2018; Peres et al., 2019; Yin et al., 2017). In oral cavity, enamel is the outermost layer and hard mineralised surface of teeth that primarily contains crystalline calcium phosphate. Enamel is typically exposed to acidic environment which disrupt the balance of the tooth enamel remineralization/demineralization processes that could result in localized destruction of hard dental tissues and formation of cavities (Arends & Ten Cate, 1981).

Normally, the rate of demineralization/remineralization on the tooth surface are balanced due to the dynamic processes that are dependent on several factors, mainly on the presence of sugar which could be fermented by cariogenic microbes, host health factors and other associated environmental factors. Dental carries starts off with the mechanism of bacteria present on the tooth surface which metabolizes sugars to produce acid that causes calcium loss from the enamel layer and gradually demineralizes the hard tissues of the teeth (Gupta et al., 2020). Prolonged acid damage on teeth, resulted in erosion and carious lesions which are the two main consequences of unbalanced demineralization-remineralization processes (Abou Neel et al., 2016). The

balance of remineralization/demineralization process is also affected by salivary flow and composition. In contrast, saliva acts as a replenishing source of minerals including calcium, phosphorus and fluoride ions which inhibits the demineralization of the enamel layer during periods of low pH and help to boost enamel remineralization when the pH returns to a neutral state.

Caries prevention at early stages from resulting in cavitated lesions requires meticulous and systematic methods for monitoring disease prior to the development of advanced lesions. Therefore, the prevention of dental caries is one of the greatest challenges in dentistry. There are vast strategies that may help to enhance oral health including improving oral hygiene practises, restricting sugar intake, and using new and effective toothpastes and toothbrushes (Bader et al., 2002). Nowadays, there has been the development of a number of innovative remineralization technologies for oral care application or dentifrices aiming at prevention of caries lesion at early stage. Due to the similar feature of biomimetic agents with natural tooth structure, great biocompatibility and its non-toxic chemical components, there is an increase of its usage in modern dentistry.

Variety of biomimetic agents have been commercialized for the treatment of early enamel carious lesion including fluoride, hydroxyapatite, and Casein Phosphopeptide-Amorphous

Calcium Phosphate (CPP-ACP) which are potentially curative regime for tooth demineralization. Fluorides are the gold standard and most prominent agent for dental caries prevention since its discovery. Fluoride compounds used in oral care are reported for its high potential in enhancing enamel remineralization process and to inhibit demineralization. Fluoride dentifrices have been extensively commercialized and found to be more efficacious for remineralization of root caries lesions (Philip, 2019). Previous study reported that toothpaste containing 1000 or 1100 ppm fluoride reduced the amount of decay in permanent teeth of children and adolescents compared with non-fluoride toothpaste (Walsh et al., 2019). However, there are raised concern of the use of high fluoride concentration in oral care products which may lead to the increases the risk of fluorosis in developing teeth (Grandjean & Landrigan, 2014). Despite fluoride-based dentifrices are effective in remineralizing enamel, they are incompetent to promote deposition of apatite nanoparticles in the enamel (Ruan & Moradian-Oldak, 2015).

Another emerging and promising biomimetic substance for oral care applications is calcium phosphate (CaP). CaPs are widely used in non-fluoride remineralizing system for their potential in preventing early caries lesions and its reparative properties towards minor enamel defects. There has been increased interest in developing bioactive agents based on CaP in oral care for enhancing enamel and dentin remineralization. Recently, vast majority of calcium phosphate remineralization systems were developed for oral care application including Casein Phosphopeptide-Amorphous Calcium Phosphate (CPP-ACP), Functionalized  $\beta$ -Tricalcium Phosphate ( $\beta$ -TCP), Calcium Sodium Phosphosilicate and Amorphous Calcium Phosphate (ACP). This bibliometric and scientometric analysis explores the interdisciplinary view of calcium phosphates-based for alternative oral care concepts in preventive dentistry. In this work, we have attempted to provide a global trend of publications and state of knowledge concerning the potential use of CaP in oral care application and preventive dentistry.

## 2. MATERIALS AND METHODS

The literatures were retrieved from the Scopus database for this bibliometric study. The chosen database covers a wide range of construction-related research. The retrieval of the publications was done on July 8, 2021. The existing literature related to calcium phosphate used in oral care research in this database was retrieved using the search parameters (( calcium AND phosphate ) AND ( dental AND caries ) AND ( remineralization )). The search period was set to include the last 10 years, from January 2011 to December 2021. The steps are shown in Figure 1.

The information for citation, bibliography, abstract, keywords, funding, and others were saved and exported in the CSV format. VOSviewer software was used to compute the scientometric analysis. This software is a tool that constructs

and visualizes bibliometric networks. The bibliometric map represents the network system of each category. The software computes the data obtained on co-authorship, abstract, keywords, multiple occurrences of keywords in the titles and citations with similar references used in the literatures and generates the bibliometric maps. The keywords frequency while generating the bibliometric maps is set at desired and any irrelevant keywords are deleted.

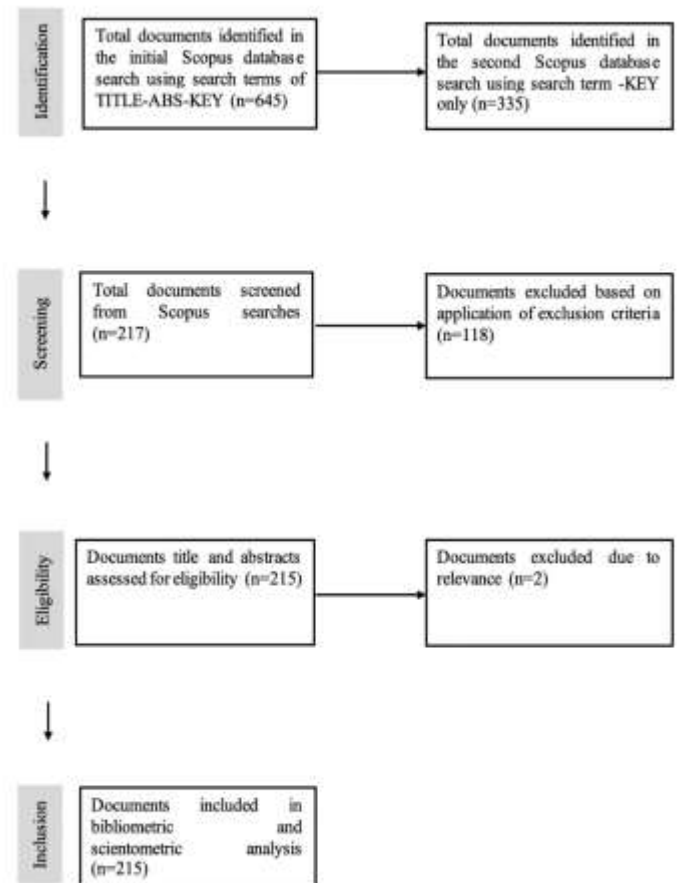


Figure 1. Steps in the bibliometric identification and screening of sources.

## 3. RESULTS AND DISCUSSION

### 3.1 Overall research trend by year of publication

To determine and visualize the current state of research on the application of calcium phosphate in oral care, publications regarding the topic including cumulative publications is plotted in a graph on a yearly basis (Figure 2). The number of publications could suggest the research patterns about calcium phosphate in oral care in the future. The research on the application of calcium phosphate in oral care was steady between 15 and 25 in 2011-2021 and the highest number of articles published in 2017. As a result, the cumulative

publication graph revealed a linear slope, indicating that academics worldwide did not pay much attention to this material's application in oral care.

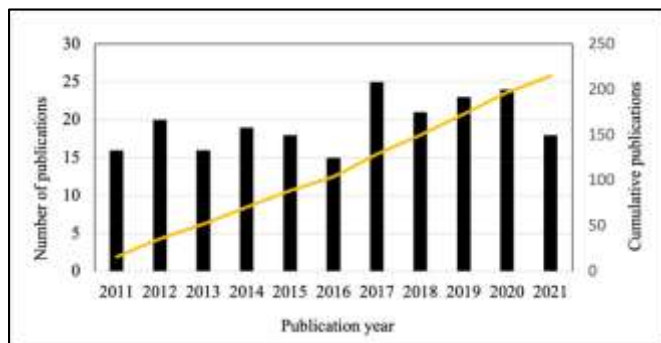


Figure 2. The number of publications and cumulative publications on a year-on-year basis

### 3.2 Country-wise distribution of publications

215 articles chosen in the analysis were published from 20 countries (Table 1). Highest number of publications can be observed coming from the United States (58 articles, 19.4% of the total documents), followed by China by 50 articles (16.7%) and India with 23 articles (7.7%). Both Australia and Brazil are in the 4th rank, with 20 articles published each (7.7%). Following that, two countries published articles in the range of 10 to 15 and 12 countries published articles in the range of three and nine. The overall number of publications is 268, which is more than the initial number 125 which shows that there is evidence on collaborative work in between the authors from different countries. Ten economically developed countries, shown by their position as a top 15 in terms of nominal GDP, have recognized the benefits of calcium phosphate in oral care. From the 58 number of publications produced, the United States had received the highest number of citations. Surprisingly, it shows that the United States was in second place (n=31) based on its average citation, followed by Italy, which had an average citation of 53 from three entire documents. Furthermore, China, United Kingdom, Thailand, and New Zealand are the countries with an average citation of 25 and higher. The links between countries collaborations on literature was also shown in Figure 3.

In order to measure the collaboration in between the countries, a point of measurement called Total Link Strength (TLS) analysis is employed. It is also shown in Figure 3 as the links between countries. The United States by far is the most collaborative country in research as showed by its TLS result of 254 (Table 1). Except for Indonesia and Singapore, the US had published documents in partnership with all of the countries listed. China obtained a TLS result of 247 which puts China in the second place. China's collaborative research was with the US, Japan, Saudi Arabia, Brazil, India, Thailand, New Zealand, Italy, the United Kingdom, and the Netherlands.

According to the TLS score and the country cooperation network map, most countries have a strong research collaboration with the US and China.

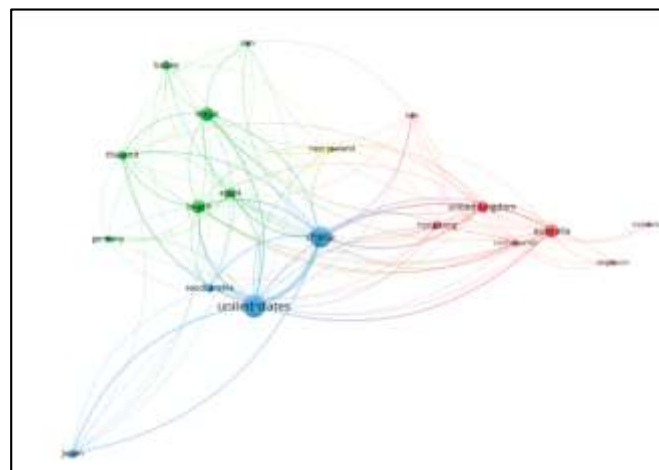


Figure 3. Country cooperation network on an application of calcium phosphate on dental caries research

### 3.3 Leading publishing organization analysis

Top organizations to have published more than three literatures are represented in Table 2. At least nine organizations had involved in publishing literatures throughout the year. The State Key Laboratory of Oral Diseases, National Clinical Research Centre for Oral Diseases, Sichuan University, Chengdu, from China had the highest number of articles published (n=13) which could bring its citations value to 574 and 50 average citations per article. After that, the Centre For Stem Cell Biology & Regenerative Medicine, School Of Medicine, University Of Maryland, Baltimore is in the second place with 11 articles published which resulted in a 207 citations value and an average of 73 citations per article. The Department Of Orthodontics, School Of Stomatology, Capital Medical University, Beijing had published eight articles with around 310 citations and 32 citations per article published. Both Department Of Advanced Oral Sciences And Therapeutics, School of Dentistry, University Of Maryland, Baltimore and Marlene And Stewart Greenebaum Cancer Center, School Of Medicine, University Of Maryland, Baltimore shared the same number of articles (n=7) published. However, there are differences in the citations and average citations per articles value. Further, the Department Of Endodontics, Periodontics And Prosthodontics, School of Dentistry, University Of Maryland, Baltimore from the United States had published five articles. This resulted in a citation value of 143 and an average of 29 citations per articles. Lastly, three organizations with two from the United States (Department Of Mechanical Engineering, University Of Maryland, Baltimore, LRM Statistical Consulting, Hoboken, New Jersey) and one from China (VIP Integrated Department, Stomatological Hospital,

Table 1: Top countries that published more than three documents

#	Country	No. of article	Percentage (%)	No. of citations	Average citations per article	Nominal GDP Rank*	Total Link Strength
1	United states	58	19.40	1786	31	1	254
2	China	50	16.72	1364	27	2	247
3	India	23	7.69	381	17	6	81
4	Australia	20	6.69	243	12	12	62
5	Brazil	20	6.69	410	21	13	76
6	United Kingdom	14	4.68	420	30	5	58
7	Egypt	10	3.34	120	12	36	57
8	Turkey	10	3.34	107	11	20	16
9	Saudi Arabia	9	3.01	112	12	19	48
10	Japan	8	2.68	135	17	3	37
11	Thailand	8	2.68	198	25	25	57
12	Hong Kong	7	2.34	155	22	40	27
13	Germany	6	2.01	97	16	4	13
14	Netherlands	5	1.67	48	10	17	24
15	Iran	4	1.34	34	9	26	16
16	New Zealand	4	1.34	106	27	50	35
17	Canada	3	1.00	54	18	9	0
18	Indonesia	3	1.00	10	3	16	3
19	Italy	3	1.00	163	54	8	18
20	Singapore	3	1.00	9	3	39	7

\* Nominal GDP Rank as per the International Monetary Fund (2019 estimates), World Economic Outlook Database, October 2019

Table 2: Top organizations that published more than three documents

#	Organization	Country	Articles	Citations	Average citations per article
1	Centre For Stem Cell Biology & Regenerative Medicine, School Of Medicine, University Of Maryland, Baltimore	United States	11	207	73
2	Department Of Advanced Oral Sciences And Therapeutics, School of Dentistry, University Of Maryland, Baltimore	United States	7	72	58
3	Department Of Endodontics, Periodontics And Prosthodontics, School of Dentistry, University Of Maryland, Baltimore	United States	5	143	39
4	Department Of Mechanical Engineering, University Of Maryland, Baltimore	United States	4	316	41
5	Marlene And Stewart Greenebaum Cancer Center, School Of Medicine, University Of Maryland, Baltimore	United States	7	296	53
6	State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases, Sichuan University, Chengdu	China	13	574	50
7	Department Of Orthodontics, School Of Stomatology, Capital Medical University, Beijing	China	8	310	32
8	LRM Statistical Consulting, Hoboken, New Jersey	United States	4	198	1
9	VIP Integrated Department, Stomatological Hospital, Jilin University, Changchun	China	4	106	29

Jilin University, Changchun) shares the same number of articles published by four articles. However, the citation and average citations of the Department Of Mechanical Engineering, University Of Maryland, Baltimore had a superior value than the other two organizations. From the analysis, it can be concluded that the State Key Laboratory of Oral Diseases, National Clinical Research Center for Oral Diseases and Sichuan University are the pioneer organisations that are involved in the research of calcium phosphate in dentistry and orthodontics.

### 3.4 Publication map cluster

Clustering techniques plays a prominent role in identifying groups of related publications and citations. To summarize, 215 publications were found and 33 of them are most frequently cited publications which were used to generate the map for publication cluster. The map visualizes how the constantly cited publications group together. Figure 4 clearly illustrates the division of the cluster in that is represented in different colours for easy visualization. To indicate the specific research topic related to the clusters identified, the 19 clusters were examined manually. Quality of the published literatures is demonstrated by the links in between the citation which suggest that the quality of a paper is influenced by its citation metrics (Table 3).

A common indication of a good quality paper is by its high citation metric. It means numerous researchers around the world have been mentioning the literature and findings in their own research. In this review, 33 documents have been selected for further analysis based on their high citation value. The most-cited document was by Weir m.d. (2012) which reported the significant level of remineralization of enamel of spray-dried amorphous calcium phosphate formulation compared to the traditional control which releases fluoride by four-fold. Second paper with the most citation is a review paper that discussed the future prospects of dental caries management strategies that utilizes functional nanoparticles which possesses antimicrobial and regenerative properties (Melo, 2013). Finally, the third most mentioned document was on the promising value of nano-HA in repairing the tooth based on its enhancement effect to the regeneration pathways of minerals (particle and ion-mediated) (Huang, 2011). Among the top three cited literatures discussed, the literatures with the most number of citations (four times) was produced by Weir m.d and Li. Both J. Weir m.d and Li. J had been cited by Liu Y, Huang S, Li J, Poggio, Robertson. It is noticeable in Figure 4 that there was one prominent and highly interrelated cluster of Weir and Li J groups. In general, it can be suggested that this cluster had represented the most significant literatures that had the most impact on calcium phosphate-based dentifrices research.

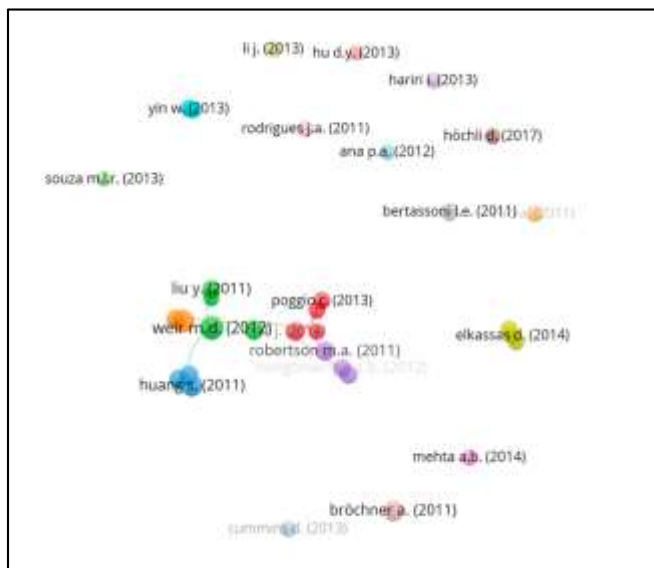


Figure 4. Documents and citations relationship of the publications that have been cited for at least forty times.

### 3.5 Distribution and co-citation relationship

The relationships between journals preferred by the authors in publishing their work is illustrated in Figure 5. The citations are important for these journals as it resembles their quality. It can be concluded that most of the authors prefers to publish their work on calcium phosphate in the Journal of Dentistry. Currently, 25 articles have been published by the journal. These articles have been cited significantly for 760 times. Second place was taken by Caries Research where 12 articles was published by the journal and with 431 citations. Journal titled Dental Materials was in the third place with ten articles publishes and 372 citations. It can be observed that these three top journals have the highest value for Total Link Strength (TLS) compared to the others. This suggest that these journals are commonly cited by authors who published their article in other journals. This can be visualized and confirmed in the source and citation relationship map generated. For the highest number of average citations, the American Journal of Orthodontics and Dentofacial Orthopaedics, Dental Materials and Caries Research were in the top three respectively. It is safe to say that the research work published in these journals are very impactful towards this area of research. This is due to the fact that these journals have a high quartile ranking. According to the Scimago database by Scopus, all the journals are in the Q1 ranking. Further, both Dental Materials (IF: 5.304) and Caries Research (IF: 4.056) are also listed as Q1 ranking in the Journal Citation Reports by Clarivate.

Table 3: Top documents that have been cited for at least forty times

#	Article	Citations	Links	Reference
1	Weir m.d. (2012)	145	4	(Weir et al., 2012)
2	Melo m.a.s. (2013)	134	2	(Melo et al., 2013)
3	Huang s. (2011)	117	1	(Huang et al., 2011)
4	Bröchner a. (2011)	94	0	(Bröchner et al., 2011)
5	Cheng l. (2015)	89	3	(Cheng et al., 2015)
6	Robertson m.a. (2011)	82	3	(Robertson et al., 2011)
7	Cheng l. (2017)	76	1	(Cheng et al., 2017)
8	Zhang l. (2016)	76	2	(Zhang et al., 2016)
9	Liu y. (2011)	75	1	(Liu et al., 2011)
10	Nongonierma a.b. (2012)	74	2	(Nongonierma & FitzGerald, 2012)
11	Li j. (2014)	73	4	(Li et al., 2014)
12	Bertassoni l.e. (2011)	73	0	(Bertassoni et al., 2011)
13	Besinis a. (2012)	72	1	(Besinis et al., 2012)
14	Jayarajan j. (2011)	72	1	(Jayarajan et al., 2011)
15	Poggio c. (2013)	62	1	(Poggio et al., 2013)
16	Yin w. (2013)	59	1	(Yin et al., 2013)
17	Elkassas d. (2014)	58	2	(Elkassas & Arafa, 2014)
18	Zhou c. (2014)	58	3	(Zhou et al., 2014)
19	Srisilapanan p. (2013)	56	1	(Srisilapanan et al., 2013)
20	Karlinsey r.l. (2012)	56	1	(Karlinsey & Pfarrer, 2012)
21	Zhang q. (2011)	56	1	(Zhang et al., 2011)
22	Weir m.d. (2017)	50	2	(31)
23	Mehta a.b. (2014)	50	0	(Mehta et al., 2014)
24	Sitthisetapong t. (2012)	50	3	(Sitthisetapong et al., 2012)
25	Ana p.a. (2012)	50	0	(Ana et al., 2012)
26	Rodrigues j.a. (2011)	50	0	(Rodrigues et al., 2011)
27	Rao a. (2011)	48	0	(Rao & Malhotra, 2011)
28	Cummins d. (2013)	47	0	(Cummins, 2013)
29	Hariri i. (2013)	46	0	(Hariri et al., 2013)
30	Li j. (2013)	45	0	(Chen et al., 2013)
31	Höchli d. (2017)	44	0	(Höchli et al., 2017)
32	Souza m.l.r. (2013)	42	0	(Souza et al., 2013)
33	Hu d.y. (2013)	41	0	(Hu et al., 2013)

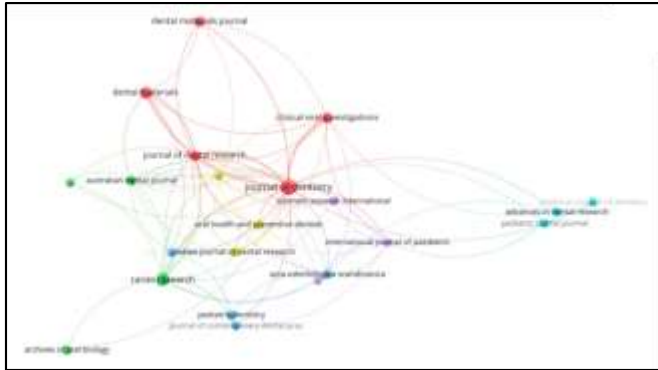


Figure 5. Source and citations relationship of the sources that published documents on an application of calcium phosphate on dental caries research.

### 3.6 Cluster density: application of calcium phosphate in oral care

A density map is generated by analyzing the co-occurrence of all keywords on calcium phosphate in oral care (Figure 6). To specifically visualize the use of calcium phosphate in dentifrice, the keywords were selected manually. The density visualization map is interpreted as such: the denser the keywords used are, the darker the yellow color and the larger the circle's size, indicates that there are more people conducting research on that specific topic. Final analysis of the density map suggests that terms such fluoride, casein and calcium phosphate are connected strongly with a variety of dentifrices used in oral application.

Dental caries is among the main issues highlighted and which draw the attention of researchers at present. A consistently increasing trend for publications over the past ten years reflects the expansion of world - wide interest in caries research. The driving factors that stimulate the growing demand in caries research are the challenges of finding appropriate treatment and prevention for dental caries. Biomimetic properties are the most popular topic discussed regarding the oral care application. According to the Scopus database, the number of publications that relate to "calcium phosphate" and "enamel remineralization" increased rapidly between 2011 (n=16) and 2021 (n=215). The trend and distribution pattern from Figure 2 indicates that research of calcium phosphate, especially studies related to teeth remineralization, is attracting increased attention from scientists and the academic community. Currently, dental substances such as fluoride, CPP and calcium phosphate are among the most common materials discussed for dentifrice formulation, due to their abundant nature, low- cost, non-toxicity, and compatibility with the applications. Previously, fluoride-based agents enhanced remineralization in the presence of critical pH, inhibit plaque glycolysis, and promote the formation of high-quality fluorapatite. Fluoride has

bactericide and bacteriostatic properties that act on microorganisms in the oral cavity, such as *Streptococcus mutans*.

In modern oral care strategies, calcium phosphates have been identified as promising biomimetic alternatives due to their similarity to natural enamel. Calcium phosphate materials are widely used as an alternative and non-fluoride agent that improve remineralization without having any possible side effects on the human body. The clinical use of calcium phosphate in caries protection shows an equal or superior efficacy in remineralization compared to fluorides and provide an efficient caries protection *in vivo*. It is assumed that calcium phosphate functions by infiltrating the micropores in early caries lesions, where it acts as crystal nuclei in the remineralization process by continuously attracting large amounts of calcium and phosphate ions from the oral fluids into the lesion, thus promoting natural remineralization processes. Besides remineralizing properties, *in situ* studies with hydroxyapatite have shown anti-adhesive properties that have the potential to be employed for a biomimetic biofilm control (Meyer et al., 2018). Microorganisms tend to attach to free hydroxyapatite particles originating from toothpaste or mouth rinse and are thus cleared from the oral cavity, since they are deprived from colonizing the enamel (Kensche et al., 2017). It is also reported that hydroxyapatite forms a protective layer on the enamel surface (Lacruz et al., 2017). Both remineralization concepts, i.e., calcium phosphates alone or in combination with fluorides have been realized in modern oral care products. However, it is important to know that combining calcium phosphates with fluorides within a toothpaste formulation may reduce the bioavailability of (ionic) fluoride in the oral cavity. This is due to the reaction of fluoride with calcium forming insoluble compounds such as Calcium Fluoride,  $\text{CaF}_2$ , or Fluorapatite  $\text{Ca}_5(\text{PO}_4)_3\text{F}$  (Epple et al., 2022).

Currently, studies on the analysis and quantification of enamel remineralization *in vivo* are still a challenge in oral care research. In general, Scanning Electron Microscopy (SEM) is ideally used to visualize morphological changes in tooth erosion whereby micro-radiography is used for advanced cases (Schlueter et al., 2011). Moving further with time, the study of biomimetics such as calcium phosphate would greatly be improved by the development of advanced methods (Pandya & Diekwisch, 2019). The most feasible part of calcium phosphate is the fact that it is abundant in wastes. For instance, remains of marine life such as clam shells, oyster, razor, sea snail shells are one of the inexpensive alternatives of hydroxyapatite and tricalcium phosphate (Terzioğlu et al., 2018). Studies on using these sources of calcium phosphate and applying it in dental care seems a promising approach in re-utilizing wastes back into the human consumption.



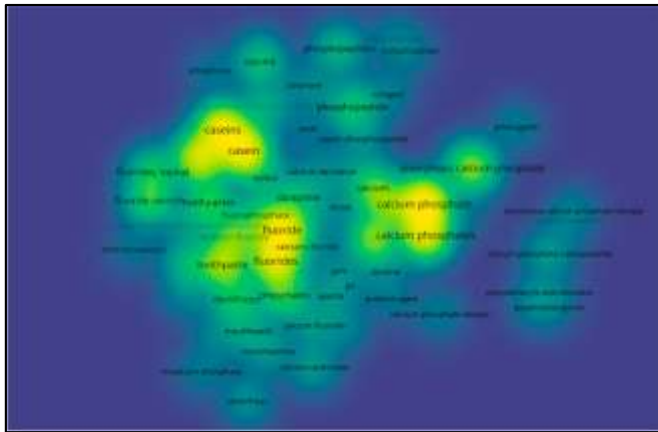


Figure 6. Density visualization map of the different elements used in dentifrice formulations.

#### 4. CONCLUSION

The current scientometrics analysis makes several important contributions to dentifrice material using calcium phosphate subject, based on a bibliometric study. In gist, the information on 215 articles related to the research area mentioned above was extracted from the Scopus database. The scientometric analysis was performed on the extracted information of the calcium phosphate materials which are currently used in dentistry and other calcium phosphate materials which have potential for dental applications. Global trends and recent publications of calcium phosphate materials in oral care application are discussed. Further, this paper had highlighted major authors and researchers who greatly contributed into the research of calcium phosphate in oral applications. Although there was major improvement and profound interest of calcium phosphate materials for dental caries research, further studies are needed to confirm their properties.

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