frontiers in Dental Medicine

SYSTEMATIC REVIEW
published: 30 August 2021
doi: 10.3389/fdmed.2021.743065

Regenerating Craniofacial Dental Defects With Calcium Phosphate Cement Scaffolds: Current Status and Innovative Scope Review

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Specialty section:
This article was submitted to Regenerative Dentistry, a section of the journal Frontiers in Dental Medicine

Received: *17 July 2021*
Accepted: *10 August 2021*
Published: *30 August 2021*

Citation:
Alsahafi RA, Mitwalli HA, Balhaddad AA, Weir MD, Xu HHK and Melo MAS (2021) Regenerating Craniofacial Dental Defects With Calcium Phosphate Cement Scaffolds: Current Status and Innovative Scope Review. Front. Dent. Med. 2:743065. doi: 10.3389/fdmed.2021.743065

The management and treatment of dental and craniofacial injuries have continued to evolve throughout the last several decades. Limitations with autograft, allograft, and synthetics created the need for more advanced approaches in tissue engineering. Calcium phosphate cements (CPC) are frequently used to repair bone defects. Since their discovery in the 1980s, extensive research has been conducted to improve their properties, and emerging evidence supports their increased application in bone tissue engineering. This review focuses on the up-to-date performance of calcium phosphate cement (CPC) scaffolds and upcoming promising dental and craniofacial bone regeneration strategies. First, we summarized the barriers encountered in CPC scaffold development. Second, we compiled the most up to date *in vitro* and *in vivo* literature. Then, we conducted a systematic search of scientific articles in MEDLINE and EMBASE to screen the related studies. Lastly, we revealed the current developments to effectively design CPC scaffolds and track the enhanced viability and therapeutic efficacy to overcome the current limitations and upcoming perspectives. Finally, we presented a timely and opportune review article focusing on the significant potential of CPC scaffolds for dental and craniofacial bone regeneration, which will be discussed thoroughly. CPC offers multiple capabilities that may be considered toward the oral defects, expecting a future outlook in nanotechnology design and performance.

Keywords: calcium phosphate, cement, scaffold, repair, regeneration, dental, craniofacial

INTRODUCTION

Following the increase in life expectancies, systematic diseases, congenital disabilities, trauma, tumor removal, and other causes of bone tissue loss (1, 2), the need for bone repair in craniofacial, dental, and orthopedic fields has increased. Each year, ∼200,000 craniofacial fractures require bone transplantation in the U.S.A., with an economic burden of $2B. Appropriate restoration of the form and function of the missing skeletal tissue is an unprecedented challenge. Defects in the craniofacial bones represent a significant emotional and economic burden as their restoration/regeneration often requires multiple complex bone grafting procedures. To address this limitation, scaffold-mediated exogenous cell transplantation and growth factors/hormone delivery are two widely-studied alternatives to conventional autologous grafts, the "gold standard." However, for therapeutic translation, both approaches encounter various barriers, including safety concerns (3–5).

The use of bone grafts to treat bone defects or regenerate a site remains a significant health challenge (6). Though autografts and allografts are used clinically, they have drawbacks such as morbidity at the donor site, disease transmission risks, and harvesting limitation (7). Different bone grafting materials have been introduced to overcome these limitations, including

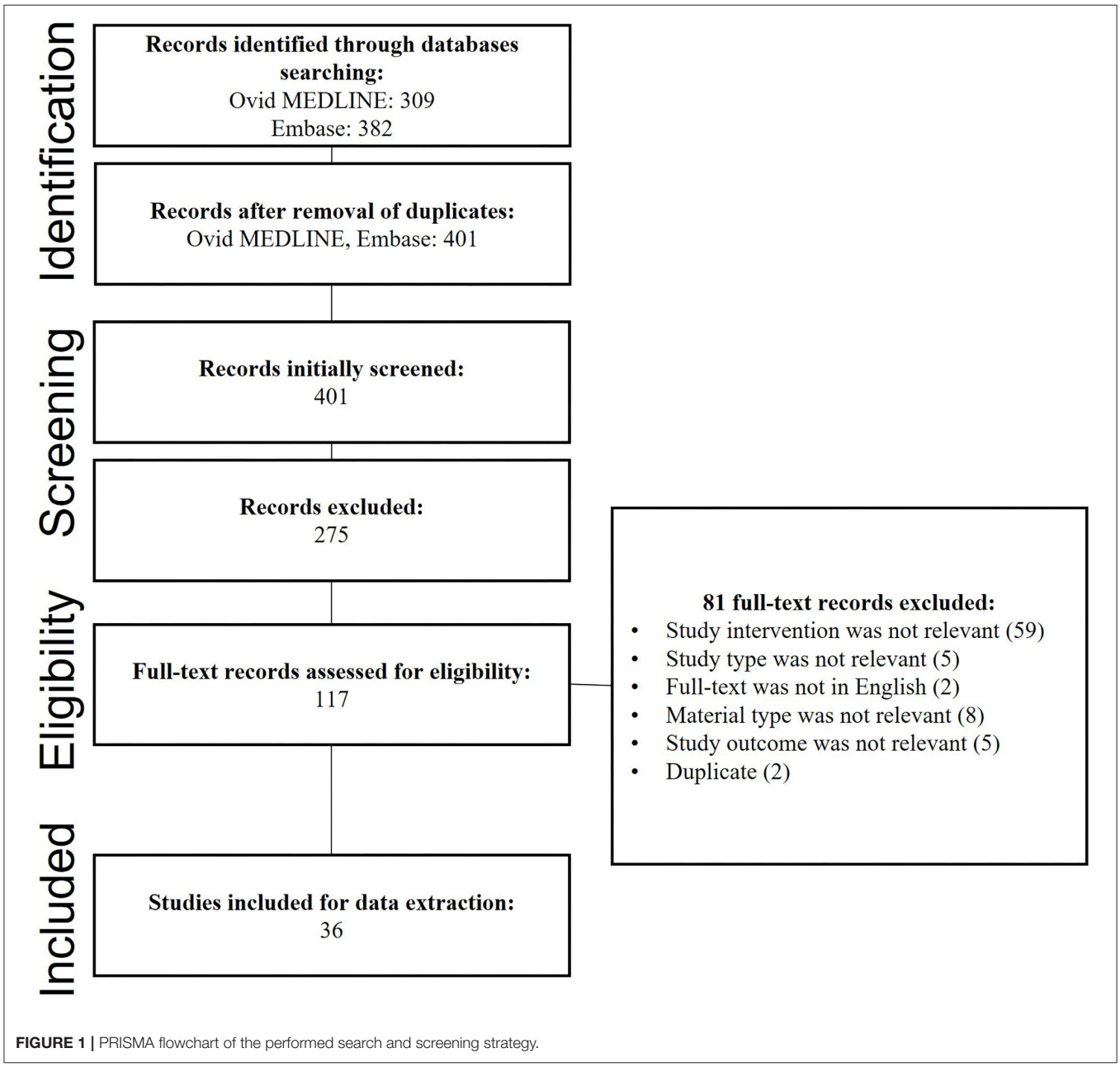

FIGURE 1 | PRISMA flowchart of the performed search and screening strategy.

biodegradable alloplastic materials such as fiber-reinforced bioactive glass materials and polymer-based polyether ketone, xenogeneic bone materials, and bioactive degradable ceramics materials like calcium phosphate and hydroxyapatite (8, 9).

Calcium phosphate ceramics have been shown to express improved bone formation and the ability to function as bone grafting substitute materials due to their osteoconductive properties and excellent biocompatibility (10–12). The literature provides a historical perspective on calcium phosphate cement (CPC) performance in many medical, craniofacial, oral surgery applications, involving augmentation of craniofacial skeletal defects, ridge recontraction, sinus augmentation, periodontal bone defects regeneration, and tooth defect regeneration (11, 13–15).

In order for prefabricated bioceramic bone grafting materials to fit into the bone defect, the operator has to modify the graft shape to the desired size or modify the surgical site. These modifications could increase postoperative trauma, bone loss, and surgical time (16). On the other hand, calcium phosphate cement (CPC) delivers intimate adaptation to bone defect contours by their ability to be injected and placed *in situ* (13). Calcium phosphate cement (CPC) consists of a combination of tetracalcium phosphate [TTCP: $Ca_4(PO_4)_2O$] and dicalcium phosphate anhydrous (DCPA:$CaHPO_4$). The CPC paste consists of CPC powder with an aqueous liquid. The resultant paste is a self-hardening paste that forms a resorbable scaffold (17). Due to its desirable biological and mechanical properties, CPC is very promising for various clinical applications. As a result, in 1996, the Food and Drug Administration approved CPC use for craniofacial defects treatments in humans (18).

The original CPC formulation was introduced in 1988 by Brown and Chow (19). A plethora of CPC formulations have been explored for their potential as a grafting material. The design is detailed-oriented, and any minor changes in the CPC formulation affect the distribution and alignment of crystalline forms in the structure (19). The Food and Drug Administration approved at least three formulations for clinical use: Bone Source®, Alpha-BSM®, and Skeletal Repair Systems (S.R.S.)®.

Since the first FDA-approved CPC for human use, a broad scope of clinical uses, including orthopedic, craniofacial, and trauma treatment, has been endorsed worldwide (20). However, intraoral clinical use of CPC has been considerably deficient. Correspondingly, scientific research focused on intraoral applications of CPC's use is also relatively scarce (20). Nevertheless, CPC scaffolds can be used with outstanding outcomes in many dental procedures due to calcium phosphate's high osteoconductivity, self-hardening properties, excellent adaptation to bone defects, and gradual resorption and replacement with a new bone (2, 6, 12). In several current publications, various *in vivo* and *in vitro* studies on the application of CPC for intraoral applications can be observed (21–23).

Therefore, this study aimed to review evidence on calcium phosphate cement (CPC) scaffolds for dental and craniofacial applications and summarize the pre-clinical, *in vivo* studies and the limited clinical studies on using CPC scaffolds treatment of oral bone defects.

MATERIALS AND METHODS

Study Design

A scoping review research technique was conducted for this review. The scoping review aims to map the currently existing literature on a complex topic or a particular topic with gaps in the literature, including the primary research characteristics, nature, and volume. Hence, the methodology used of literature scoping was carried on calcium phosphate cement (CPC) scaffolds for dental and craniofacial bone regeneration (19). For our scoping review, a 5-stage framework was adopted following Arskey and O'Malley's design (20), and the recommendations conducted by Levac, Colquhoun, and O'Brien were embraced (21). This approach includes a team with an iterative process for study selection and qualitative data assessment. The five stages involved: research question identification, identification of relevant results, selection of studies, data charting, and results reporting.

Stage I: Identification of Research Question

The aim was to answer two key questions for this research: "*What are the main types of calcium phosphate cement (CPC) scaffolds that are mostly investigated for dental/ craniofacial regeneration*" and "*What are the modifications and additive components for those scaffolds or cements that imparted enhanced performance*?"

Stage II: Identification of Pertinent Studies

A research library supported the databases search for subject terms, keywords, and text words related to studies that evaluated bone regeneration using calcium phosphate cement (CPC) scaffolds for dental and craniofacial applications. Two independent researchers reviewed the related articles (RA and HM) using EMBASE, and Medline (OVID) databases. The search strategy performed for MEDLINE was followed for EMBASE and revised properly to account for the syntax rules and vocabulary differences.

Terms searched were related to the calcium phosphate cement (CPC) scaffolds used and involved but were not limited to calcium phosphate or $CaPo_4$, dental or craniofacial, scaffolds, cements, regeneration, or repair. To ensure the quality assessment of the found resources. The searches were limited to peer-reviewed journals. Searches were also limited to English language articles from 2000 to 2020. **Figure 1** demonstrates the studies' search procedure using PRISMA flowchart.

Stage III: Selection of Studies

The criteria for studies inclusion were established by researchers (RA and HM) throughout stages II and III. The following inclusion criteria were followed: (1) references from peer-reviewed journals; (2) references that studied calcium phosphate materials for bone regeneration (including cements and scaffolds); (3) references that evaluated the bone regeneration of calcium phosphate cements or scaffolds for dental and craniofacial applications; (4) references with the publication year 2000-current; (5) references with the English language were selected.

TABLE 1 | The detailed characteristics and outcomes of the included studies.

References	Type of study	Composition of C.P.C.	Adjunctive materials	Type of defect	Outcomes
Sugawara et al. (24)	*In vivo* (animal study-Beagle dogs)	TTCP + DCPA (1:1)	N/A	Alveolar bone defect	The histological evaluation revealed a new bone formation after 6 months from placing the CPC compound
Shirakata et al. (21)	*In vivo* (animal study-Beagle dogs)	α-TCP, calcium carbonate, and monocalciumphosphate monohydrate mixed with a solution of sodium phosphate	N/A	Fenestrations and periodontal defects	No significant difference was observed between the use of CPC compound and control in treating the defect
Fujikawa et al. (25)	*In vivo* (animal study-Beagle dogs)	TTCP + DCPA (1:1)	N/A	Alveolar bone defect	Natural bone augmentation around the implant observed 6 months following the surgery
Sorensen et al. (26)	*In vivo* (animal study-Hound labrador mongrels dogs)	DPCP (The Ceredex^{TM} Type 2)	Recombinant human BMP2	Alveolar bone and periodontal defects	A higher amount of cementum was observed compared to the control but with no oriented periodontal ligaments and a high possibility of ankylosis and root resorption, which may limit its use
Xu et al. (27)	*In vitro*	TTCP + DCPA (1:1)	Chitosan	-	The CPC-chitosan system was capable of inducing nanosized hydroxyapatite crystals like that found in teeth and bone
Masago et al. (28)	*In vivo* (animal study-Albino rabbits)	β-TCP	Titanium fibers added to platelet-Rich-Plasma	Alveolar bone defect	An expressive quantity of new viable bone was observed after 5 months compared to the control
Shirakata et al. (29)	*In vivo* (animal study-Beagle dogs)	α-TCP, monocalcium phosphate monohydrate, and calcium carbonate mixed with a solution of sodium phosphate	Enamel matrix derivative (E.M.D.)	Periodontal defect	CPC with EMD. produced a greater bone and cementum formation compared to the use of EMD. alone or the use of open flap debridement
Xu et al. (30)	*In vitro*	TTCP + DCPA (1:1)	Absorbable fibers, biopolymer chitosan, and mannitol porogen	-	High capabilities in delivering osteogenic cells and Osteoinductive growth factors to promote bone regeneration
Arisan et al. (31)	*In vivo* (animal study-Beagle dogs)	TCP	N/A	Dental implant-related defect	No differences were found in the bone-to-implant contact percentage and bone height between the CPC and the control with no treatment
Aral et al. (32)	*In vivo* (animal study-sheep)	TCP	N/A	Maxillary sinus defect	The bone formation around the placed implants in the CPC group was similar to the group that received autologous bone
Fei et al. (33)	*In vitro*	TTCP + DCPA (1:1)	Bio-degradable BMP-2 loaded PLGA microspheres	-	Rabbit marrow stromal cells revealed osteogenic activities when treated with the CPC/BMB-2/PLGA system
Um et al. (34)	*In vivo* (animal study-Beagle dogs)	Biphasic hydroxyapatite and calcium phosphate glass (HA/CPG)	Bovine serum albumin	Periodontal defect	The CPC-albumin revealed more significant new bone formation, cementum regeneration, and bone area compared to the control but with no difference in the group without albumin
Mellonig et al. (35)	Clinical study (case series)	Powdered monocalcium phosphate monohydrate, α-TCP, and calcium carbonate with a solution of sodium phosphate (Norian®)	N/A	Periodontal defect	Clinical and histological healing of the defects was evident, but no periodontal regeneration was observed
Weir and Xu (36)	*In vitro*	TTCP + DCPA (1:1)	Chitosan	-	Human mesenchymal stem cells successfully differentiated into osteogenic lineage when they were seeded onto the CPC-chitosan system

(Continued)

TABLE 1 | Continued

References	Type of study	Composition of C.P.C.	Adjunctive materials	Type of defect	Outcomes
Thein-Han et al. (37)	*In vitro*	TTCP	Type I collagen fiber and alginate hydrogel microbeads	-	hUCMSCs on CPC with collagen demonstrated higher osteogenic expression compared to CPC without collagen
Wang et al. (38)	*In vivo* (animal study-Beagle dogs)	TTCP + DCPA (1:1)	BMP-2, fibroblast growth factor, and bone marrow stromal cells	Dental implant-related bone defect	Higher bone mineralization was observed compared when the adjunctive agents were combined all with the CPC compared to the other groups
Thein-Han et al. (39)	*In vitro*	TTCP	RGD peptides, human fibronectin, FEPP, E.M.G., and HPC	-	The hUCMSCs on C.P.C.s functionalized with R.G.D., human fibronectin, FEPP, E.M.G., or HPC significantly had better cell attachment, proliferation, actin fiber expression, osteogenic differentiation and mineral synthesis, compared to the traditional CPC control
Shih et al. (40)	*In vivo* (animal study-Beagle dogs)	Calcium sulfate dihydrate	Hydroxyapatite	Alveolar bone defect	CPC and hydroxyapatite at the 50/50 revealed more new bone volume compared to no treatment following the extraction
Shirakata et al. (41)	*In vivo* (animal study-Beagle dogs)	α-TCP, monocalcium phosphate monohydrate, and calcium carbonate in sodium phosphate solution	E.M.D.	Periodontal defect	The highest bone formation was observed in the CPC and EMD group compared to the other groups
Oortgiesen et al. (13)	*In vivo* (animal study-Wistar rats)	α-TCP (85%), DCPA (10%), and hydroxyapatite (5%)	E.M.D.	Periodontal defect	50% more bone formation was achieved in the CPC-EMD group compared to the EMD. alone
Khojasteh et al. (42)	*In vivo* (animal study-Mongrel dogs)	Polycaprolactone-TCP	M.S.C.s	Mandible bone defect	A higher bone formation was observed with the incorporation of the M.S.C.s
Chen et al. (43)	*In vitro*	TTCP + DCPA (1:1)	RGD-modified chitosan	-	hESCs seeded onto the CPC-RGD/chitosan system expressed high osteogenic markers, including alkaline phosphatase, osteocalcin, collagen I, and Runx2. The mineral synthesis on the CPC-chitosan-RGD scaffold was twice that for CPC-chitosan control
Ohayon (23)	Clinical study	Biphasic calcium phosphate (BCP) composed of 60% hydroxyapatite (H.A.) and 40% β-tricalcium phosphate (β-TCP)	N/A	Maxillary sinus defect	Six months following the surgery, the bone samples mean composition harvested from the grafted sinuses was 26.1% newly formed bone, 29.3% remaining BCP particles, and 44.7% connective tissue and bone marrow
Oortgiesen et al. (22)	*In vivo* (animal study-Wistar rats)	α-TCP, DCPA, and hydroxyapatite	BMP-2 or fibroblast growth factor-2	Periodontal defect	CPC with BMB-2 or FGF-2 revealed better periodontal healing compared CPC alone. Only the CPC + FGF-2 demonstrated a significant difference in increasing the bone healing
Tang et al. (44)	*In vitro*	TTCP + DCPA (1:1)	N/A	-	Induced pluripotent stem cells derived mesenchymal stem cells seeded onto the CPC showed good viability and osteogenic differentiation on CPC scaffold, which may allow bone regeneration in dental and orthopedic fields
Chen et al. (45)	*In vitro*	TTCP + DCPA (1:1)	RGD and chitosan	-	The CPC-RGD-chitosan system increased the genes expressions of osteogenic and angiogenic differentiation markers of the treated human umbilical vein endothelial cells and human osteoblasts

(Continued)

TABLE 1 | Continued

References	Type of study	Composition of C.P.C.	Adjunctive materials	Type of defect	Outcomes
Wang et al. (46)	*In vitro*	TTCP + DCPA (1:1)	Hydrogel alginate-fibrin fibers encapsulating stem hiPSCs, hESCs, hUCMSCs with chitosan	-	All three cells demonstrated high alkaline phosphatase, runt-related transcription factor, collagen I, and osteocalcin expressions
Wang et al. (47)	*In vivo* (animal study-New Zealand white rabbits)	TTCP and calcium hydrogen phosphate (1:1)	Osteoinductive neuropeptide substance P (S.P.) and collagen type I	Alveolar bone defect	CPC and SP with collagen achieved thicker and denser bone compared to the CPC alone and the other tested groups
Wongsupa et al. (48)	*In vitro*	Biphasic calcium phosphate	Poly-ε-caprolactone polymer and human dental pulp stem cells	-	The CPC system demonstrated excellent osteogenic capabilities, good cells' viability, and alkaline phosphatase markers were observed
Zhao et al. (49)	*In vivo* (animal study-goats)	β-TCP	Deciduous tooth stem cells	Maxillary sinus defect	A higher bone formation was observed when β-TCP was combined with DTSCs compared to β-TCP alone or the use of autogenous bone
Kamal et al. (50)	*In vivo* (animal study-New Zealand white rabbits)	β-TCP	Composite xenogenic dentine particles	Alveolar bone defect	Defects treated with composite dentinβ-TCP combined with xenogenic dentine particles significantly demonstrated higher bone volume fraction, bone mineral density, and percentage residual graft volume compared to β-TCP alone
Carlisle et al. (51)	*In vivo* (animal study-Sinclair minipigs)	Scaffold containing polyurethane and a hydroxyapatite/β-tricalcium phosphate	Recombinant human BMP-2	Mandible bone defect	Complete bone formation was achieved in the CPC/BMP-2 group with low inflammatory markers
Xia et al. (52)	*In vitro*	TTCP	Iron oxide nanoparticles	-	The osteogenic differentiation of hDPSCs was markedly enhanced via IONP incorporation into C.P.C.
Helder et al. (53)	Clinical study	Biphasic calcium phosphate (BCP)	-	Maxillary sinus defect	The use of BCP20/80 in human MSFE resulted in a higher bone and osteoid volume than BCP60/40, but no differences in vascularization could be observed
Fakheran et al. (54)	*In vivo* (animal study-Beagle dogs)	β-tricalcium phosphate	Mineral trioxide aggregate and collagen membrane	Periodontal defect	A higher bone and cementum formation compared to the use of the collagen membrane or mineral trioxide aggregate alone
Xia et al. (55)	*In vitro*	TTCP + DCPA (1:3)	Iron oxide nanoparticles and chitosan	-	The incorporation of iron oxide nanoparticles into CPC scaffold significantly enhanced the spreading, osteogenic differentiation, and bone mineral synthesis of human dental pulp stem cells (hDPSCs)
Naujokat et al. (56)	*In vivo* (animal study-Miniature pigs)	Biphasic calcium phosphate (BCP)	N/A	Dental implant-related defect	Scaffold achieved better bone-to-implant contact percentage, inter-thread bone densities, and peri-implant bone compared to the groups treated with hydroxyapatite or titanium

BMP2, Bone morphogenetic protein-2; EMD, Enamel matrix derivative; PLGA, Poly(lactic-co-glycolic acid); RGD, Arginylglycylaspartic acid; FEPP, Fibronectin-like engineered polymer protein; EMG, Extracellular matrix Geltrex; HPC, Human platelet concentrate; hiPSCs, Human induced pluripotent stem cells; hESCs, Human embryonic stem cells; MSCs, Mesenchymal stem cells; hUCMSCs, Human umbilical cord MSCs.

Exclusion criteria were: (1) references with publication year prior to 2000; (2) references published in languages other than English. Screening of the references was made by reading the abstracts and titles. Then it was determined by each independent reviewer if the reference were to be considered for revision of the full text. Based on this screening, a final agreement was reached following the divergences of reviewers, and the assessment of full-text stages was established.

Stage IV: Data Charting

A spreadsheet software was used to create a template for data extraction. The template was established and reviewed by each

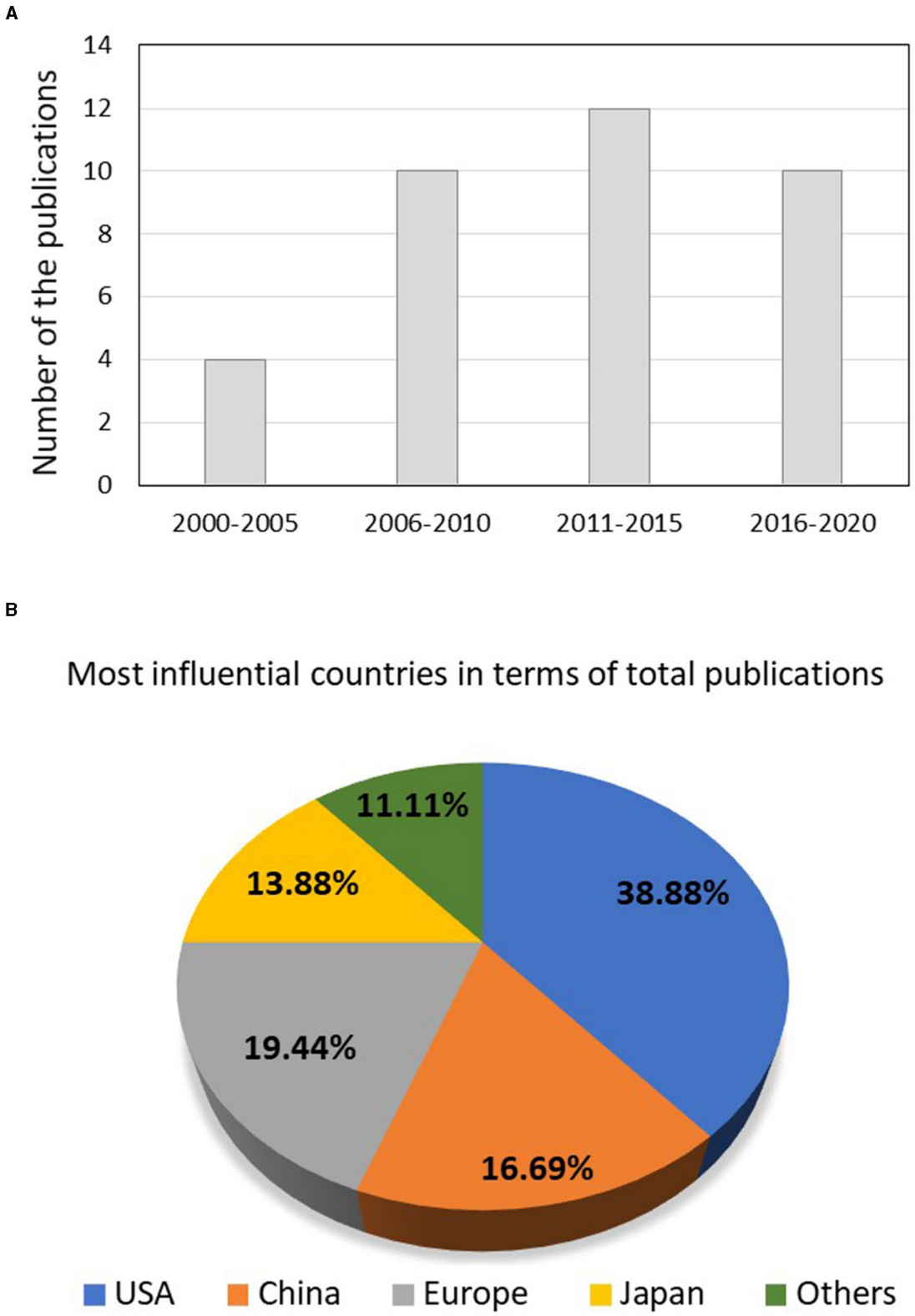

FIGURE 2 | (A) The number of publications performed from 2000 to till 2021 concerning the use of calcium phosphate scaffolds in dentistry and **(B)** the most influential countries in terms of total publications.

author. The reviewers were calibrated on answering the research questions and recording the variables to be extracted. The extracted data from all studies included was made by (RA, HM, and AAB).

Stage V: Extraction of Data and Results Reporting

The extracted data from the included references were done by the first three authors (RA, HM, and AAB). Data were arranged according to (1) name; (2) date published; (3) country of origin; (4) study type (*in vivo* or *in vitro*); (5) calcium phosphate type used; (6) other materials incorporated into the cement or scaffold; and (7) any other modifications made to the calcium phosphate scaffolds and the reason behind any modifications.

RESULTS

Articles' Distribution

Out of the 401 studies, 36 articles that investigated the potential use of CPC for dental tissue engineering and regeneration were included. **Table 1** illustrates the detailed characteristics and outcomes of the included studies. **Figure 2A** illustrates the increasing number of the published articles related to the subject from 2006 and 2020. 38.88% of the studies were conducted in the United States of America (U.S.A.), 30.57% were published in China and Japan, and 19.44% were published in European countries as shown in **Figure 2B**.

The Type of the Study and the Investigated CPC

Most of the investigations were *in vivo* studies (58.33%) that utilized an animal model to study the effect of the CPC on tissue engineering and regeneration. Only 5.60% of the articles were clinical studies, while the remaining were *in vitro,* as displayed in **Figure 3A**. The most investigated CPC was tricalcium phosphate TCP (35.16%), in its two forms α-TCP and β-TCP, followed by the TTCP+DCPA mixture (32.43%) as displayed in **Figure 3B**. TTCP was used alone in around 10.81% of the included studies. The use of other calcium phosphate compounds such as biphasic calcium phosphate and calcium sulfate dehydrate was also reported. 35.13% of the studies focused on bone regeneration in general, 24.32% on periodontal and soft tissue regeneration, and 18.91% on alveolar bone regeneration, as displayed in **Figure 3C**.

Adjunctive Incorporated Materials

Twenty seven out of the 36 studies had incorporated other materials with the CPC compounds. 21.27% of the incorporated materials are represented by growth factors, platelet-rich plasma (PRP), or proteins. Mesenchymal, stem, and differentiated cells composed 10.63% of the incorporated materials, and 19.14% were represented by polymeric materials, as illustrated in **Figure 4A.** Other materials such as hydrogels, clot-forming materials, hard or soft tissue derivatives, peptides, and fibers were also reported. Around 72.43% of these adjunctive materials were incorporated to improve tissue engineering and bone regeneration capabilities, as shown in **Figure 4B.**

DISCUSSION

This study sought to review evidence on calcium phosphate cement (CPC) scaffolds for dental applications and summarizes the pre-clinical, *in vivo* studies and the limited clinical studies on the use of CPC scaffolds to treat dental bone defects. This report's findings have elicited a better understanding of: (1) The main types of calcium phosphate cements scaffolds used in the dental/craniofacial field; (2) What are the modifications and additive components for those scaffolds or cements that imparted enhanced performance over nearly 20 years of research.

CPC shows promising bone replacement capability, osteoconductivity, self-hardening properties and is shown to be used in several intraoral procedures, including bone ridge augmentation, implant grafting, periodontal regeneration, and sinus lift augmentation (**Figure 5**) (20, 31, 41, 51). An appropriate CPC type should be used to achieve optimum clinical outcomes. Each type of CPC has a different resorption rate, and each proposed clinical use required a different resorption rate. For some applications such as periodontal bone defect repairs and sinus lift, the capability of the grafted cement to be replaced quickly by bone is highly desirable.

On the other hand, other uses such as cranioplasty, graft stability, and integrity are more important than rapid resorption and replacement by bone (20). Using a different type of calcium phosphate as the significant element of CPC could provide an applicable method for formulating a cement with a different range of resorption rates. Depending on the cement setting reaction, different types of cement systems demonstrate different pH setting characteristics. Therefore, a CPC with a specific pH level should be used to gain compatibility with other components, such as antibiotics, growth factors, and osteoinductive factors (2).

In this scoping review, the most investigated CPC composition was TCP (35.13%), in its two forms, α-TCP, and β-TCP. TCP is a resorbable phase of calcium phosphate with a Ca/P ratio of 1.5. It has also been shown to help in bone growth. TCP cement helps in maintaining bony defect spaces and permits bone growth on their surface or into channels, pores, or pipes, and primarily acts as osteoconductive materials (57). The α and β phases have the same chemical composition, but they have different crystalline structures and solubility. The α-TCP has a monoclinic crystalline structure, and the β-TCP has a rhombohedral crystalline structure.

Both types of TCP are stable at room temperature in the absence of humidity; however, α-TCP has shown lower stability of the crystal lattice compared to β-TCP in a density functional study. Therefore, α-TCP can be hydrolyzed and be more reactive in aqueous systems than β-TCP. Similarly, α-TCP is used as a component of CPC, although α-TCP never occurs in biological calcifications (58, 59). In the field of dentistry, α-TCP is used primarily as a fine powder to prepare calcium phosphate cements due to its high solubility and reactivity, which makes it ideally used as injectable biodegradable cements (59). However, the main drawbacks that limit the use of α-TCP in its pure form in biomedical applications are its rapid resorption rate which

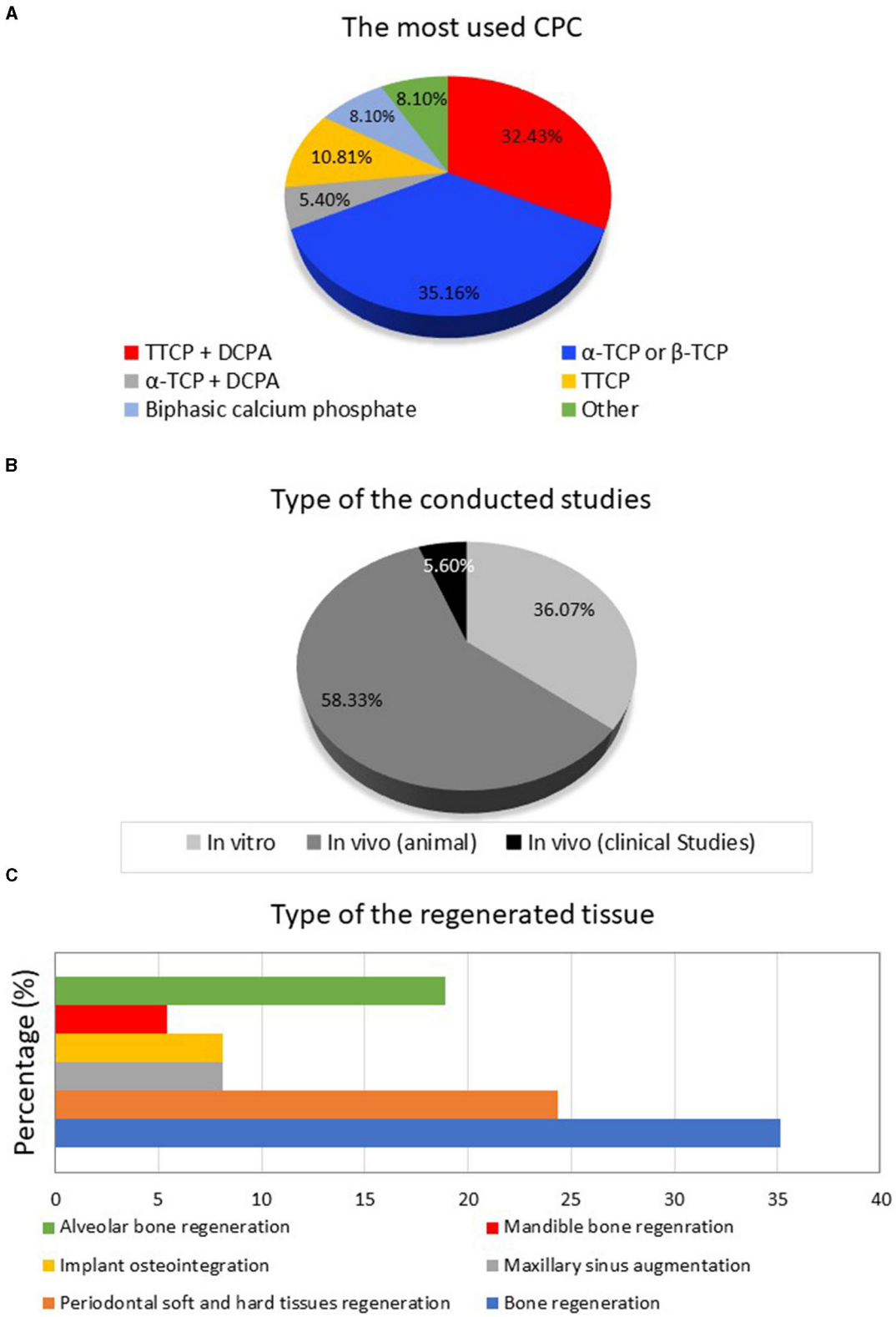

FIGURE 3 | (A) The types of the included studies, **(B)** the different types of calcium phosphate compounds, and **(C)** the targeted regenerated dental tissues.

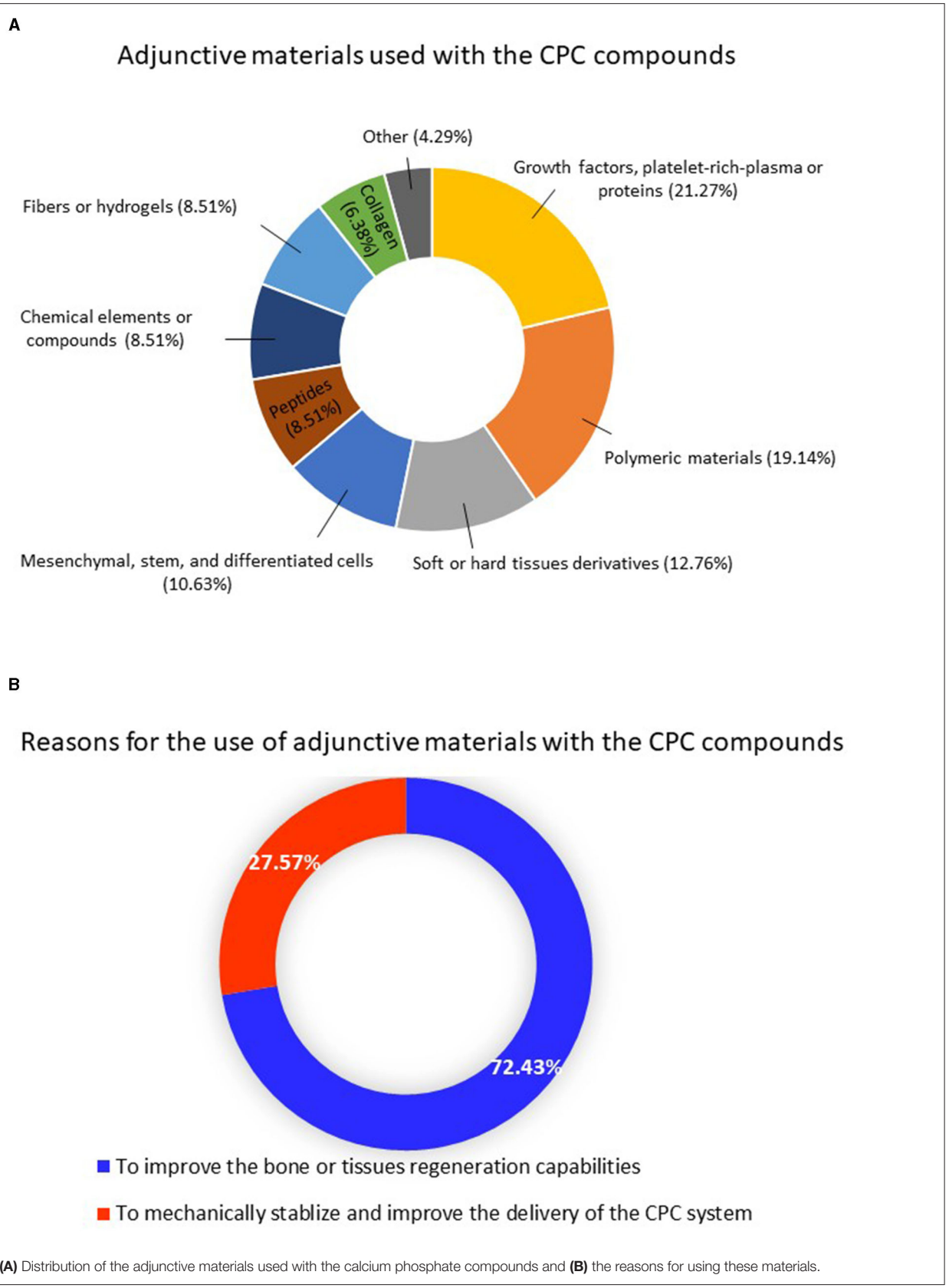

FIGURE 4 | (A) Distribution of the adjunctive materials used with the calcium phosphate compounds and **(B)** the reasons for using these materials.

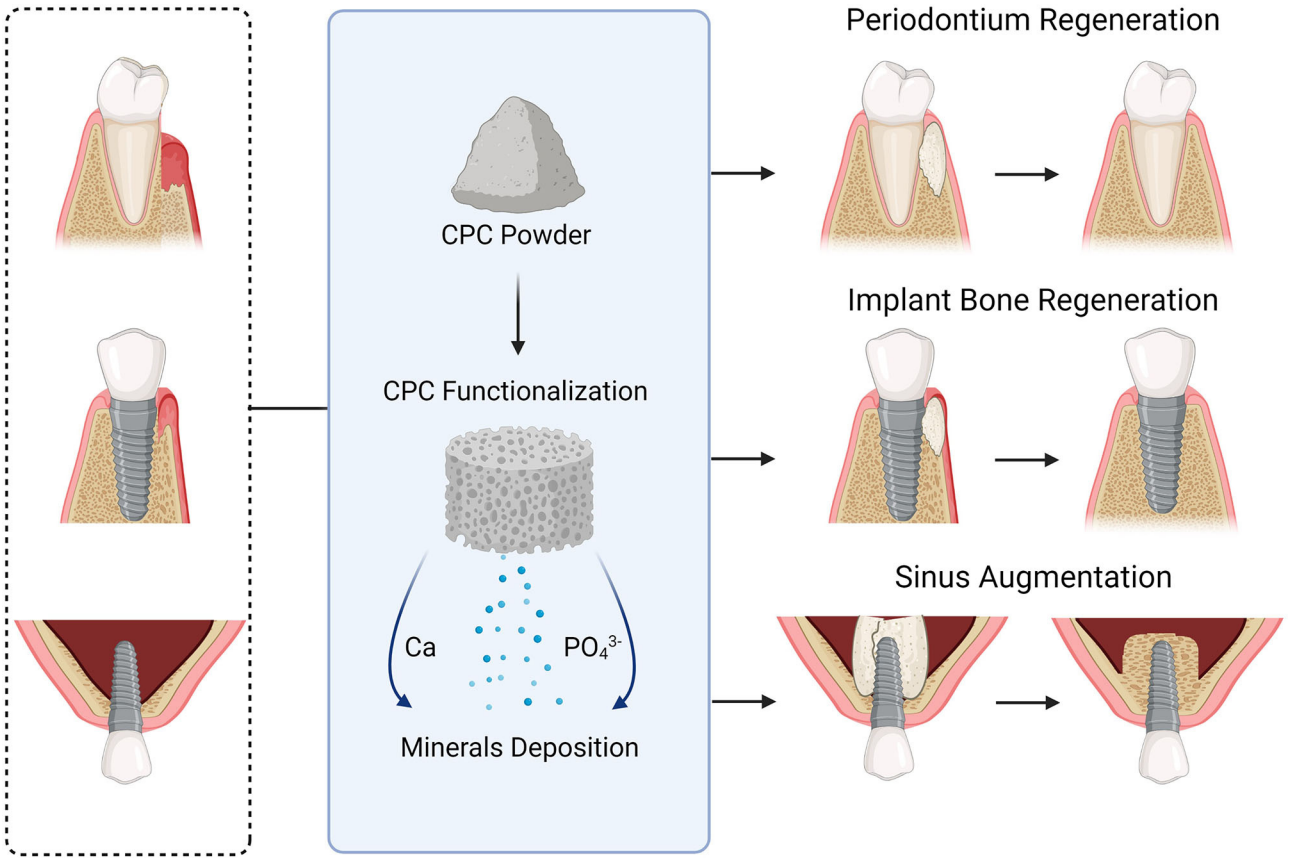

FIGURE 5 | A schematic drawing illustrates some calcium phosphate compounds applications to regenerate soft and hard dental tissues.

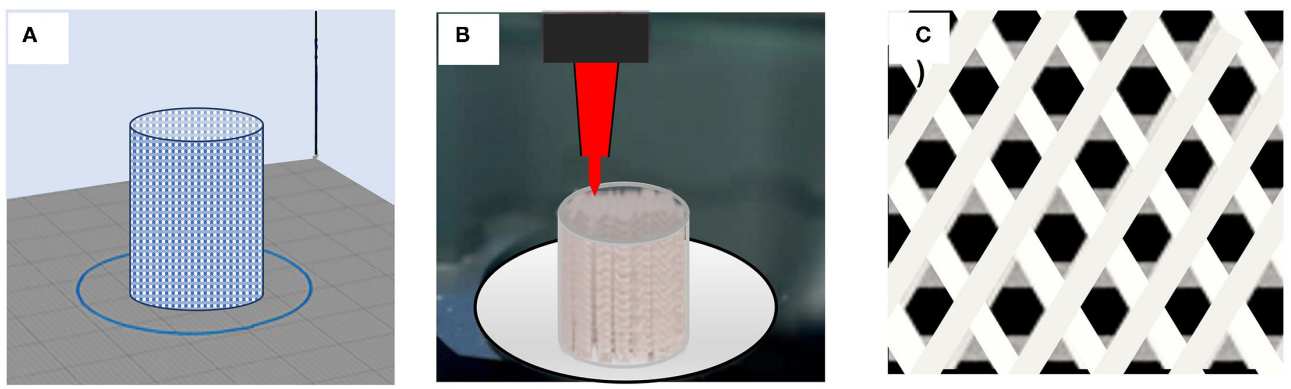

FIGURE 6 | Illustration of structure and fabrication process of a 3D-printed calcium phosphate scaffold. **(A,B)** Design and printing stage of a calcium phosphate scaffold. **(C)** 3D-printed scaffolds structure.

is faster than the formation of a new bone, and its limited mechanical properties (60).

Meanwhile, β-TCP has a resorption rate slower than α-TCP. Therefore, β-TCP preserves the structural stability for a longer time compared to α-TCP. Also, it has excellent cell adhesion and biomineralization attributes. However, β-TCP has several drawbacks when used as an osteoconductive cement. First, the new bone absorption rate does not entirely match with the β-TCP absorption rate. As a result, new bone absorption is slightly faster than β-TCP absorption. Second, it has slight brittleness and poor mechanical properties, which limits its use in weight-bearing areas. Moreover, β-TCP lacks osteogenicity and osteoinductivity (2, 20, 58). Previous *in vivo* results showed very limited osteogenesis outcomes of β-TCP (61).

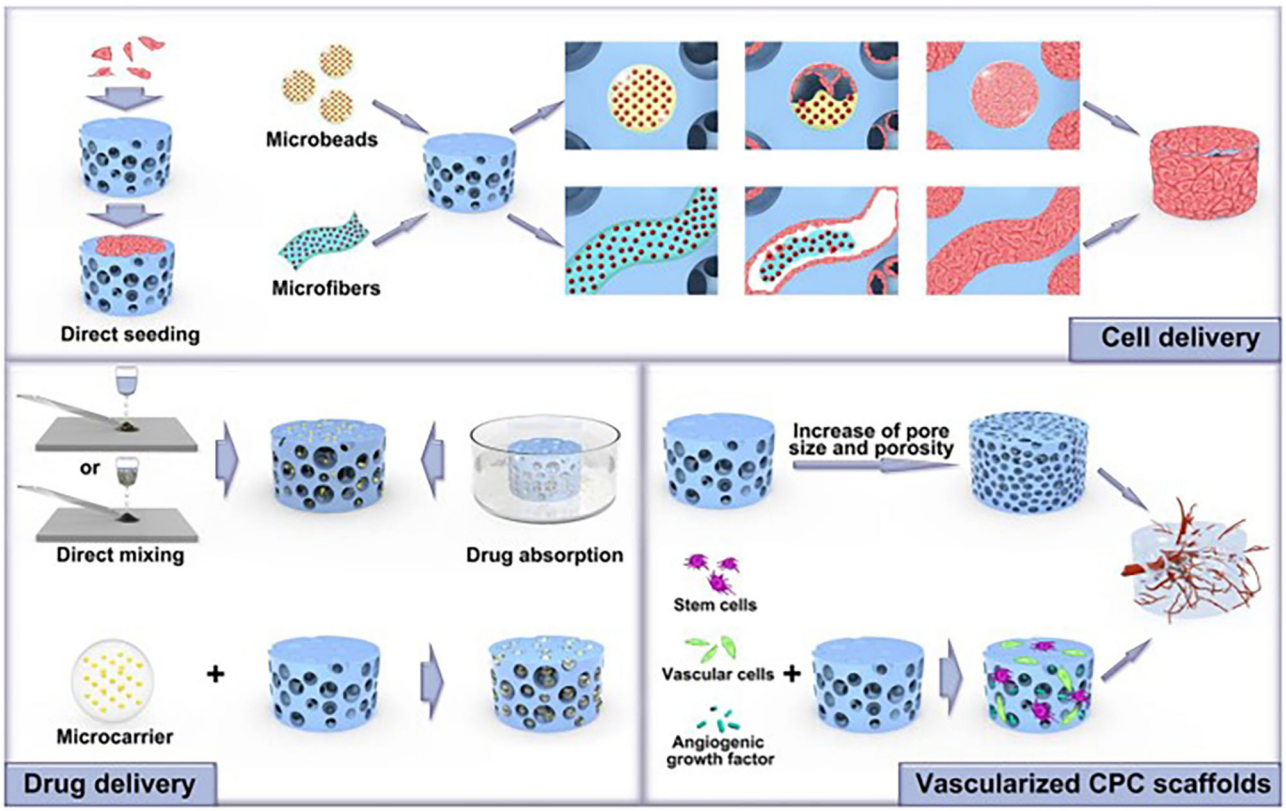

FIGURE 7 | Various promising new advancements in CPC technologies and their major biological properties could be applied in the dental field to enhance bone and periodontal regeneration success rates. Adapted from Xu et al. (70).

To improve the physical and biological properties and address the limitations of β-TCP, some adjunctive materials have been used to form β-TCP based CPC. These adjunctive materials involve osteogenic materials (bone marrow and mesenchymal stem cells), osteoconductive materials [hydroxyapatite (HA) and poly-caprolactone (PCL)], and bone-induced materials [platelet-rich plasma (PRP), and bone morphogenetic protein-2 (BMP-2)]. Moreover, to regulate β-TCP resorption rate, the activity of osteoclasts or osteoblasts can be regulated by the addition of metal ions such as Si and Zn (58).

In this scoping study, TCP was most commonly used to treat periodontal defects, followed by alveolar bone and bony defects around the dental implant. β-TCP was commonly used for alveolar bone defects and dental implant defects regeneration, while α-TCP was mainly used for periodontal regeneration. None of the studies compared the regeneration outcome of α-TCP and β-TCP. More studies are needed to find the best TCP-based CPC type for treating each intraoral defect type.

The second most investigated CPC type was the TTCP+DCPA mixture. TTCP is the most basic calcium phosphate and the most soluble calcium phosphate below a pH of 5 (62). TTCP shows poor biodegradability despite its high solubility and remains unreacted in an aqueous environment at room temperature for a long time. TTCP forms a thin, insoluble HA layer coating its particles and inhibiting further degradation, and this could be attributed to its low reactivity (63). On the other hand, DCPA is considered an acidic calcium phosphate. When mixing DCPA with TTCP, an acid-base reaction to form a poorly-crystalline hydroxyapatite is created (64). Under neutral pH environments, both types are much more soluble than HA.

Moreover, a slurry containing a mixture of DCPA-TTCP can generate a constant amount of HA precipitation without changing the composition of the solution (2). Previous observation found that aqueous pastes of DCPA+TTCP mixtures converted to a solid mass when remaining in test tubes for several hours. As a result, the first type of self-hardening cement that formed HA as a by-product and consisted of only calcium phosphates was discovered (64). This DCPA+TTCP composition became the first commercially available CPC for use in humans and received approval from the US Food and Drug Administration in 1996 (20).

Traditional DCPA+TTCP based CPC has self-setting properties and is an *in situ* hardening paste that can be injected or sculpted to bony defects during surgery. However, traditional DCPA+TTCP based CPC showed limited mechanical, physical, and biological properties (65, 66). Therefore, different approaches have been used to overcome these limitations, such as the incorporation of chitosan, absorbable fibers, biofunctionalization, mannitol porogens, gas-foaming agents, and alginate microbeads (65–67). These methods enhanced the CPC's setting time, mechanical strength, degradability,

macroporosity, delivery of cells, growth factors, and improved cell attachments.

Different methods to enhance traditional CPC properties have been reported (27, 33, 43, 55). Chitosan had been used with DCPA+TTCP based CPC and could create a non-rigid cement that possesses high strength and durability compared to traditional CPC (27). Other studies showed that encapsulation of pluripotent-derived mesenchymal stem cells and BMP-2 on DCPA+TTCP based CPC significantly enhanced bone regeneration and achieved a 2–3 fold increase in bone regeneration compared to CPC control without cell delivery (33). When human dental pulp stem cells and human bone marrow stem cells were seeded into DCPA+TTCP based CPC *in vitro,* it showed excellent cell attachment, osteogenic differentiation, mineralization, and new bone and blood vessels were formed. In addition, seeding stem cells into CPC increased new bone formation and new blood vessel density (43). Moreover, in another study, the osteogenic differentiation of human dental pulp stem cells was considerably improved via iron oxide nanoparticles incorporation into CPC. The incorporation of iron oxide nanoparticles into the CPC scaffold significantly enhanced osteogenic differentiation and bone mineral synthesis (55).

Another promising calcium phosphate grafting material is biphasic calcium phosphate (BCP). It consists of hydroxyapatite (HA) and ß-tricalcium phosphate (ß-TCP). The chemical composition of BCP mimics the inorganic part of the natural bone matrix. ß-TCP degrades faster and has a different resorption pattern than HA, since HA is rigid, brittle, and has limited resorption after application (56, 68). For effective graft remodeling, there should be an appropriate balance between the resorption rate of the graft materials and the growth of new bone formation. BCP with a HA to ß-TCP ratio of 60:40 shows the slowest resorption rate of BCP currently used in clinics, whereas a bone graft with 100% ß-TCP has the fastest resorption rate and may resorb before new bone formation (53).

Most recently, Naujokat et al. evaluated the osseointegration of dental implants in ectopic engineered bone flaps in three different scaffold materials: HA, BCP, and titanium. Radiographic, histological, and histomorphometric analysis showed that all implants exhibited sufficient primary stability, and the success rate was 100%. The bone-to-implant contact ratios (BICs), the inter-thread bone densities, and the peri-implant bone-scaffold densities were higher in BCP than HA and titanium. The BIC exhibited a strong correlation ($r = 0.76$) with the density of the peri-implant bone scaffolds. However, BCP was not reported to be used as a calcium phosphate cement; it was reported to be used as a scaffold only (53, 68).

It is essential to highlight that most of the included reports were *in vivo* studies that applied an animal model. Such an observation indicates that different animal models are well-described in the literature. As a result, future investigations are encouraged to design randomized clinical trials to illustrate the clinical effectiveness of CPC scaffolds among patients. In addition, some limitations were found in the reported investigations, such as controls that involved no intervention (31). Therefore, the studied CPC scaffolds should be compared to a control with gold-standard intervention concerning the targeted dental bone in order to identify the clinical advantages of such treatment. Furthermore, most of the investigations were conducted using one type of CPC. While other factors such as the site of application and the compound's pH may play a role in selecting the CPC compound, studies that compared different types of CPC materials are needed.

The use of adjunctive materials to improve the stability or the regeneration capabilities was reported in most of the included studies. Such findings indicate that the CPC materials could be tuned to different nanoplatforms, stem cells, or growth factors to elicit better clinical outcomes. Bone regeneration is typically a long process; therefore, other materials to support the stability and control the release of the CPC compounds are essential to improve its success (69). In **Table 1**, it can be observed that using adjunctive material with the CPC compounds was, most of the time, beneficial in improving the bone regeneration capabilities compared to the use of CPC alone. More studies are needed to investigate and apply the new advancements in CPC technologies and focuses on innovative biological synergies of CPCs on the different applications of the oral cavity procedure **Figures 6**, **7** (70). The major current progress in CPCs, involving stem cell delivery, 3D printing, growth factor, drug delivery, and pre-vascularization of CPC scaffolds, is a promising field to enhance the success rate of bone and periodontal regeneration in the oral cavity. Future investigations are encouraged to explore different strategies and approaches to support the bone regeneration of the CPC materials. In this scoping review, only Medline and Embrace databases were used. As a result, more databases are recommended to add more eligible articles and create a more comprehensive search. Future meta-analysis is recommended to critically evaluate and statistically combine results of studies or trials of comparable outcome.

CONCLUDING REMARKS

Within the outcomes of this scoping review, researchers could use the existing information on CPC combined with the new innovative methods to develop a new CPC scaffold type that can fully meet each dental use requirement. However, more *in vivo* and *in vitro* studies need to be conducted to determine the functional efficacy of the material for each dental application. CPC was successfully used in different oral applications, including periodontal regeneration, alveolar ridge augmentation, sinus lifting graft, and dental implant-related bony defects. For each clinical application, the requirements of the CPC material vary significantly. Therefore, it should not be expected that only one CPC formulation can be universally efficient. More studies are needed in order to draw a clear map of the necessary properties of each CPC materials type to meet the essential requirement for each dental application.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

All authors contributed in desgining and writing this manuscript. All authors have read and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fdmed.2021.743065/full#supplementary-material

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