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Editorial

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Biomedical and Bioengineering Prospects of Calcium Phosphates

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Calcium phosphates are a group of materials that have shown tremendous potential for biomedical and bioengineering applications. The most attractive aspect of these materials is their ability to mimic natural bone's chemical and physical properties, making them ideal for use in orthopedic, dental, and tissue engineering applications. In this editorial, we will discuss the biomedical and bioengineering prospects of calcium phosphates, along with the challenges associated with their research, and technology transfer toward clinical applications.

One of the most promising applications of calcium phosphates is in bone tissue engineering. Bone is a complex tissue, which undergoes continuous remodeling throughout life. The vast research performed so far on the bone tissue engineering aspects of calcium phosphates clearly demonstrate their capability of enhancing bone regeneration and repair. Moreover, calcium phosphates are biocompatible, osteoconductive, and bioresorbable; therefore, they can be integrated into the surrounding tissues and eventually replaced by new bone tissue.

Calcium phosphates can also be used in the field of dentistry. Tooth enamel is composed of calcium phosphate, and the use of calcium phosphate-based materials in dental applications has been shown to improve the strength and durability of dental restorations[1]. Additionally, calcium phosphates have antibacterial properties, making them ideal for dental materials that can prevent and treat dental infections. Another potential application of calcium phosphates is in drug delivery[2]. Calcium phosphates can be used as carriers for drugs, allowing targeted drug delivery to specific tissues or organs. This approach can reduce the side effects of drugs and improve their therapeutic efficacy. Calcium phosphates also have potential applications in the treatment of cancer. Calcium phosphate nanoparticles have been shown to be effective in delivering anticancer drugs to tumor cells, reducing the toxicity of the drugs to healthy tissues, and improving the efficacy of cancer treatments[3].

As can be seen, calcium phosphates have tremendous potential for biomedical and bioengineering applications[4], such as bone tissue engineering, dentistry, drug delivery, and cancer treatment[5]. Therefore, continued research and development in this field will undoubtedly lead to new and innovative uses for these versatile materials, ultimately improving human health and quality of life.

1. Patents in the Field of Calcium Phosphate Research

A substantial number of patents have been registered worldwide during the past 20 years on different aspects of calcium phosphates. Majority of them covered the following aspects:

❑ Synthesis and processing methods for calcium phosphate materials

❑ Medical devices and implants containing calcium phosphate materials

❑ Methods for coating or modifying the surface of calcium phosphate materials

❑ Compositions and formulations containing calcium phosphate materials used in drug delivery or tissue engineering applications

❑ Methods for using calcium phosphate materials in bone regeneration or repair

It is worth noting that the patents are granted on country-by-country basis, and the process of obtaining a patent can be lengthy and expensive. Additionally, patents may expire after a certain period, which means that the technology described in the patent may become available for public use. Transfer of calcium phosphate-based technologies is facing several challenges, including regulatory approval, scale-up and manufacturing, intellectual property, clinical adoption, and reimbursement. Some important patents registered in the field of calcium-phosphate research are listed in **Table 1**.

Table 1. Some important patents registered in the field of calcium-phosphates and their applications.

Sl. No.	Description	Patent Number & Year of publication
1	Calcium phosphate/calcium silicate cement for biomedical applications	WO2012007612A1 (2012-01-19)
2	Bone graft materials and methods	US9220596B2 (2015-12-29)
3	Calcium phosphate cements and methods for using the same	US10022471B2 (2018-07-17)
4	Deposition-conversion method for tunable calcium phosphate coatings on substrates and apparatus prepared thereof	US10926000B2 (2021-02-23)
5	Biomaterials Containing Calcium Phosphate	US20140155904A1 (2016-08-23)
6	Calcium phosphate microgranules	US7326464B2 (2008-02-05)
7	Production method for calcium phosphate nanoparticles with high purity and their use	EP2041025A2 (2009-04-01)
8	Preparation of calcium phosphates	US3467495A (1969-09-16)
9	Method of preparing calcium phosphates	US2906602A (1959-09-29)
10	Solid calcium phosphate materials	WO1988009769A1 (1988-12-15)
11	Method for making a porous calcium phosphate article	US20050186353A1 (2006-08-01)
12	Bone regeneration materials based on combinations of monetite and other bioactive calcium and silicon compounds	EP2396046B1 (2012-06-13)
13	Inorganic shaped bodies and methods for their production and use	US8303976B2 (2012-11-06)
14	Production of calcium phosphates and calcium nitrate	US2609271A (1952-09-02)
15	Method for producing calcium phosphates	US4166839A (1979-09-04)

2. Status of Calcium Phosphate Research Worldwide

While the research on calcium phosphates and their applications has been carried out worldwide, below we are listing the countries and laboratories where substantial developments and notable investments have been made.

Research on calcium phosphate has been conducted in various regions around the world, including America, Asia, the Middle East, Europe, and Oceania. The extent of research conducted in each of these regions is graphically depicted in **Figure 1**.

American continent: The research on calcium phosphate in the American continent has focused on its potential applications in bone regeneration, dental applications, drug delivery, and biomineralization. Many of the studies have been conducted in the United States, Canada, Mexico, and Brazil with researchers from institutions such as the University of California, Los Angeles, Harvard University, and the University of Toronto. The research has led to the development of calcium phosphate-based materials for bone grafts, implants, and coatings of orthopedic implants. Additionally, calcium phosphate has been studied for its potential use in tooth remineralization, prevention of tooth decay, and as a material for drug delivery.

Asian continent: Calcium phosphate research in Asia has been focused on bio-ceramics, dental applications, drug delivery, and biomineralization. Researchers in Japan, China, India, South Korea, and Singapore have conducted numerous studies on the use of calcium phosphate-based materials for bone regeneration and coatings of orthopedic implants. Additionally, calcium phosphate has been investigated for its use in tooth remineralization and as a material for drug delivery. Studies on biomineralization have also been conducted, with researchers investigating both the formation of calcium phosphate minerals in living organisms and using calcium phosphate to mimic biomineralization processes in synthetic materials.

Middle East: Research on calcium phosphate in the Middle East has focused on its potential applications for bone regeneration, dental applications, and drug delivery. Researchers from Israel, Iran, Turkey, and Saudi Arabia have conducted studies into the use of calcium phosphate-based materials for bone grafts and implants. Additionally, calcium phosphate has been investigated for use in tooth remineralization and as a material for drug delivery.

European continent: Research on calcium phosphate in Europe has focused on its potential applications in bone regeneration, dental applications, drug delivery, and biomineralization. Researchers in the United Kingdom, Germany, Spain, and France have conducted numerous studies on the use of calcium phosphate-based materials for bone grafts, implants, and coatings on orthopedic implants. Additionally, calcium phosphate has been investigated for its potential use in tooth remineralization, the prevention of tooth decay, and as a material for drug delivery. Studies on biomineralization have also been conducted, with researchers investigating the formation of calcium phosphate minerals in living organisms and using calcium phosphate to mimic biomineralization processes in synthetic materials.

Oceania continent: Research on calcium phosphate in Oceania has focused on its potential applications in bone regeneration and dental applications. Researchers in Australia and New Zealand have conducted studies on the use of calcium phosphate-based materials for bone grafts, implants, and coatings on orthopedic implants. Additionally, calcium phosphate has been investigated for its potential use in tooth remineralization and the prevention of tooth decay.

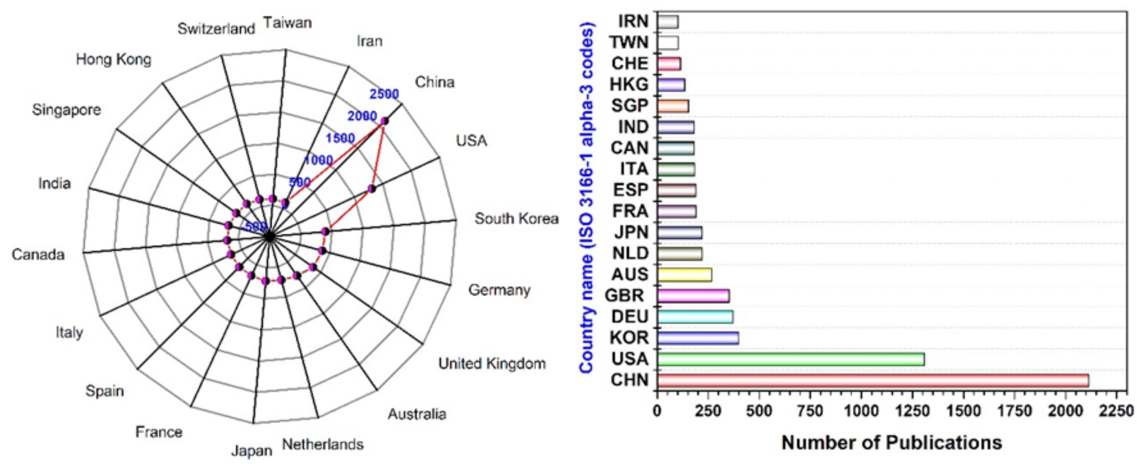

Figure 1. Country-wise research article published on Calcium phosphate for biomedical application. Collected from SCOPUS data, searched using key words "Calcium Phosphate Biomedical Application" dated 30th April 2023.

Calcium phosphate research has been conducted extensively, with researchers investigating its properties and potential applications in various fields and regions around the world. The research has led to the development of new materials that have potential applications for bone regeneration, dental applications, and drug delivery, as well as a better understanding of biomineralization processes[6,7]. Some of the specific aspects of this research that are currently being focused worldwide include:

Bone regeneration: Calcium phosphate-based materials have been extensively studied for their ability to promote bone regeneration[8]. Researchers worldwide are working on developing new calcium phosphate-based bone graft substitutes and coatings for orthopedic implants that can stimulate bone growth and improve implant stability[9].

Drug delivery: Calcium phosphate-based nanoparticles have shown promise as drug delivery vehicles[10]. Researchers are exploring the use of these nanoparticles to deliver a range of therapeutics, including anti-cancer drugs, growth factors, and antibiotics[11].

Tissue engineering: Calcium phosphate-based materials are also being studied for their potential use in tissue engineering[12]. Researchers are working on developing calcium phosphate-based scaffolds and matrices that can support the growth of various types of tissues, including bone, cartilage, and skin.

Dental applications: Calcium phosphate-based materials have also been investigated for their potential use in dental applications[13]. Researchers are developing new calcium phosphate-based dental materials that can promote the regeneration of tooth enamel, dentin, and pulp. They are also studying the use of calcium phosphate-based materials in periodontal therapy and oral drug delivery.

Antibacterial properties: Calcium phosphate-based materials have been shown to have inherent antibacterial properties, which make them promising candidates for use in implant coatings and wound dressings[14]. Researchers are investigating ways to enhance these antibacterial properties and develop new materials that can combat antibiotic-resistant bacteria.

Biocompatibility: The biocompatibility of calcium phosphate-based materials is a key factor in their success for biomedical applications[15]. Researchers are studying the interactions between these materials and the body, and developing new materials that can better integrate with the surrounding tissue and promote healing.

Biomineralization: Biomineralization is a process in which living organisms create minerals with specific shapes and structures[16]. Researchers are studying the biomineralization process and developing new approaches to synthesize calcium phosphate-based materials with biomimetic properties. They are also exploring the use of these materials in the development of bioinspired materials for biomedical applications.

3. Current Challenges in Calcium Phosphate Research

While calcium phosphates show great promise for biomedical and bioengineering applications, there are also several challenges that researchers face in doing research in this field. The challenges of calcium phosphate-related research include:

❑ *Controlling the properties of calcium phosphate materials:* The properties of calcium phosphate materials, such as their crystal structure, porosity, and surface area, have a significant impact on their biological performance. However, controlling these properties is challenging, and there is still room for research on how to optimize the properties of calcium phosphate materials for specific applications.

❑ *Improving the mechanical properties of calcium phosphate materials:* Although calcium phosphate materials have excellent biocompatibility, osteoconductivity, and bio-resorbability, they often lack the mechanical strength required for load bearing applications. Developing calcium phosphate materials with improved mechanical properties remains a significant challenge.

❑ *Enhancing the bioactivity of calcium phosphate materials:* Although calcium phosphate materials are osteoconductive, their ability to promote new bone formation is limited. Researchers are investigating ways to enhance the bioactivity of calcium phosphate materials; for example, by incorporating growth factors, peptides, or other bioactive molecules.

❑ *Developing new synthesis methods:* Conventional synthetic processes of calcium phosphate materials are complex and often involve high temperature and harsh chemical conditions. Developing new synthesis methods that are more environmentally friendly, energy-efficient, and scalable are a significant challenge.

❑ *Translating research into clinical applications:* While there have been many promising preclinical studies on the use of calcium phosphates in biomedical and bioengineering applications, translating these findings into clinical applications remains a significant challenge. Researchers need to address regulatory and safety concerns, develop robust manufacturing processes, and demonstrate the clinical efficacy and safety of calcium phosphate-based products.

In conclusion, while there are significant challenges in calcium phosphate related research, the potential benefits of these materials make them a compelling area of study. Overcoming these challenges will require continued research and collaboration across disciplines and sectors, as well as investment in technology development and transfer. The challenges in technology transfer for the clinical application of calcium phosphate-based technologies (devices) are:

❑ **Regulatory approval:** One of the major challenges in technology transfer is obtaining regulatory approval from governing bodies such as the US Food and Drug Administration (FDA). These agencies require extensive safety and efficacy testing to ensure that the technology is safe and effective for human use. The regulatory process can be time-consuming and expensive, and failure to obtain approval can result in significant delays and setbacks for technology transfer.

❑ **Scale-up and manufacturing:** Another challenge in technology transfer is the scale-up and manufacturing of the technology. Processes that work well in the laboratory may not be scalable to the commercial level, and manufacturing processes must be carefully designed to ensure consistency and quality. In the case of calcium phosphate-based technologies, manufacturing of devices can be complex, requiring precise control of factors such as particle size, porosity, and mechanical properties.

❑ **Intellectual property:** Protecting intellectual property is critical for technology transfer, as it can be a key factor in attracting investment and securing licensing agreements. Patent thickets refer to the situation where multiple patents cover a single technology, making it difficult for researchers to develop new technologies without infringing on someone's patent rights. In the field of calcium phosphate research, several patents cover some common aspects of technology, leading to patent thickets that can impede research and development. Nevertheless, obtaining patents for technologies based on calcium phosphate is sometimes difficult due to previous instances in the field or due to the apparent obviousness of the technology.

❑ **Clinical adoption:** Even after regulatory approval and manufacturing, there might be challenges in clinical adoption of calcium phosphate-based technologies. Clinicians are frequently reluctant to adopt new technologies they are not familiar with and are concerned about their safety and efficacy. It can take time to build clinical experience and establish the value of a new technology.

❑ **Reimbursement:** Finally, reimbursement can be a significant challenge for technology transfer. Even if a calcium phosphate-based technology is approved by regulatory agencies and adopted by clinicians, reimbursement policies may not cover the cost of the device or may not adequately compensate for its use. This can limit the adoption and result in limited market penetration.

Overcoming these challenges requires a combination of scientific expertise, business acumen, and persistence. While the process of technology transfer can be complex and time-consuming, the potential benefits for patients and the healthcare system make it a worthwhile endeavor.

4. Future Prospects of Calcium Phosphates

The future prospects of calcium phosphates in biomedical and bioengineering applications are vast and promising. Some potential areas of growth and development in using calcium phosphate materials are: i) *Advanced bone grafts*: Calcium phosphates have already been used as bone grafts, but advancements in the field could lead to the development of more sophisticated and advanced bone grafts. For instance, researchers are exploring the use of three-dimensional printing to create personalized bone grafts that are optimized for a patient's unique anatomy. ii) *Regenerative medicine:* Calcium phosphates have the potential to be used in regenerative medicine to repair and replace damaged tissues and organs. Researchers are exploring the use of calcium phosphates in tissue engineering, which involves growing new tissues in a laboratory that can be implanted in the body to replace damaged tissues. iii) *Drug delivery*: Calcium phosphates have been used as carriers for drugs, and future developments could lead to the creation of more sophisticated drug delivery systems. For instance, researchers are exploring the use of calcium phosphate nanoparticles as carriers of drugs that can target specific cells or tissues in the body. iv) *Dental applications*: Calcium phosphates have been used in dental applications, such as remineralization of teeth and the prevention of tooth decay. Future developments in the field could lead to the creation of new, improved dental materials that are more effective in preventing and treating oral health problems. v) *Biomineralization*: Researchers are also exploring the potentials of using calcium phosphates in biomineralization processes, which involve the formation of mineral structures in living organisms. Understanding and mimicking these processes can lead to the development of new materials and technologies for a range of applications.

5. Conclusion

The biomedical and bioengineering prospects of calcium phosphates are undoubtedly promising. Over the years, extensive research has been carried out on the properties, characteristics, and potential applications of calcium phosphates in medicine and biotechnology. From bone grafts and dental applications to drug delivery and biomineralization, calcium phosphates have been utilized in a wide range of applications. One of the key strengths of calcium phosphates is their biocompatibility, which means they can be used in medical applications without causing adverse effects or rejection by the body. Furthermore, the properties of calcium phosphates can be modified to suit different applications, making them versatile and adaptable to different needs. However, despite the potential benefits of calcium phosphates, there are still challenges that need to be addressed. One of the main challenges is the synthesis of calcium phosphates with optimum properties and characteristics, for specific applications. Additionally, there is a need for more research on the long-term safety and efficacy of calcium phosphates in clinical applications. Regulatory approval for the use of calcium phosphates in medical applications is also a substantial challenge. This requires rigorous testing and validation to ensure that the materials are safe and effective, which can be time-consuming and expensive. In conclusion, the biomedical and bioengineering prospects of calcium phosphates are promising, but further research and development are necessary to optimize their properties and functionalities. Addressing the challenges and limitations associated with calcium phosphates could lead to the creation of new and innovative materials and technologies that can impact human health and well-being significantly.

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