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REVIEW

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# Advancements of biomaterials in oral tissue engineering: past, present, and future

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## Abstract

**Background** The deformation of oral and maxillofacial region leads to not only the damage of morphology and function, but also a series of aesthetic and psychological problems, severely affecting the quality of life of patients. Oral tissue engineering refers to developing biomaterials for repair or regeneration, with the application of tissue engineering technologies. This has become an area of increasing prominence. Current biologically inert materials are insufficient to fulfill clinical requirements. Therefore, tissue-engineered biomaterials with bioactive, even bionic properties are desperately needed.

**Main body** The complexity of the anatomy and the diversity of tissue types of oral and maxillofacial region pose great challenges to the regeneration, in the aspects of both biomaterials and manufacturing technologies. Biomaterials in clinical practice or research have evolved from natural materials to synthetic materials, from homogeneous materials to multiple composite materials. And now composite materials have increasingly demonstrated their advantages in terms of physicochemical and biological properties over conventional materials. In terms of manufacturing, traditional coating, sintering, and milling technologies can no longer satisfy the requirements for high-precision bionic structures of oral-tissue-engineering biomaterials. Scientists have turned to biofabrication technologies such as microfluidics and additive manufacturing.

**Short conclusion** This review aims to summarize the noteworthy advancements made in biomaterials of oral tissue engineering. We outlined the current biomaterials and manufacturing technologies and focused on various applications of these materials that may be connected to clinical treatment and research. We also suggested the future direction of development for biomaterials in oral tissue engineering. In future, biomaterials characterized by precision, functionalization, and individualization will be manufactured through digital, microfluidic, and 3D printing technologies.

**Keywords** Oral medicine, Tissue engineering, Regenerative medicine, Biocompatible materials, Biomimetics

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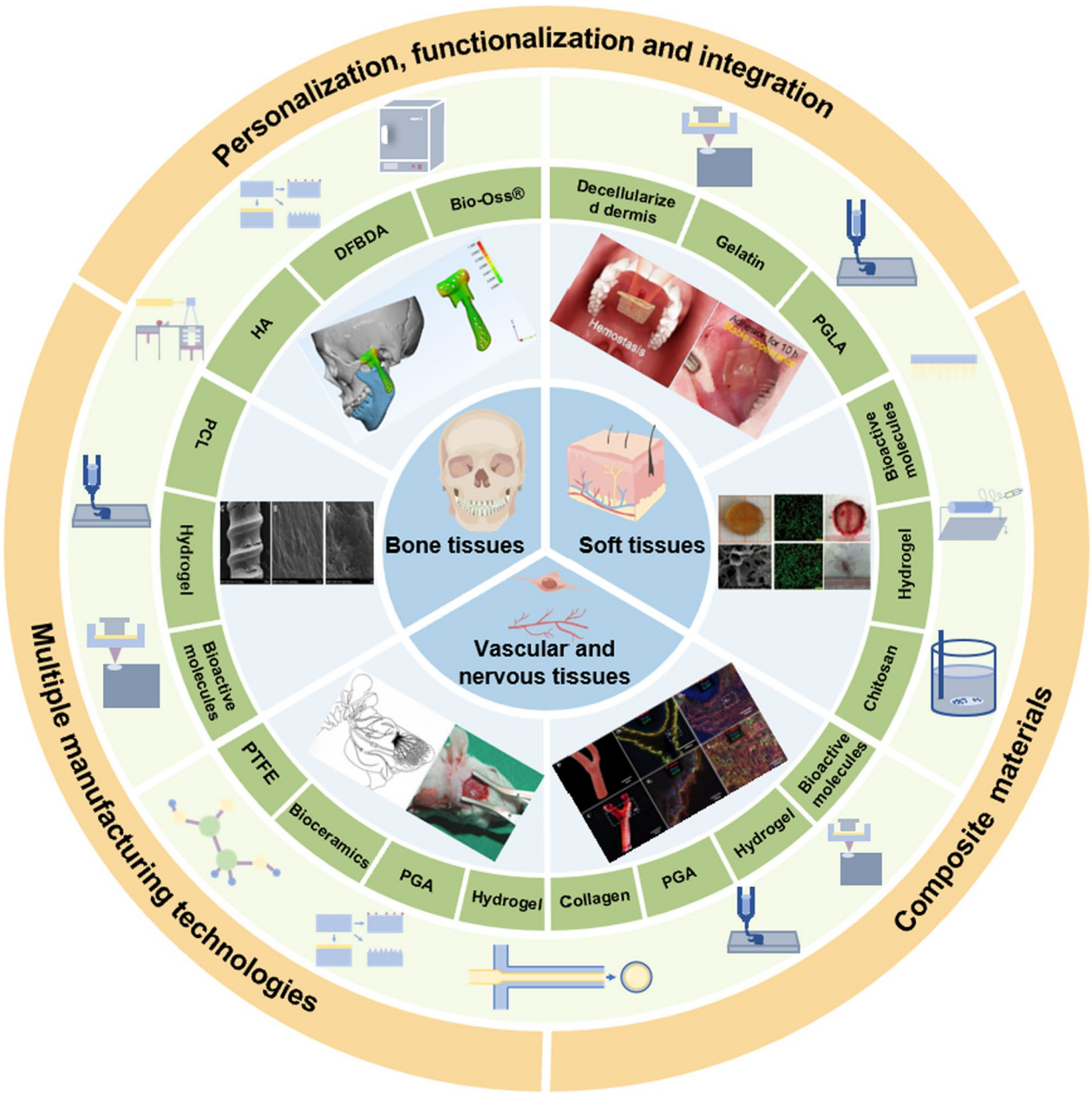
**Graphical abstract**




## 1 Background

The oral and maxillofacial tissues include organs that are exposed to the surface and extremely vulnerable to trauma, such as jaws, tongue, and teeth [1]. Infection and trauma-induced soft tissues and bone defects are the main causes of oral and maxillofacial deformities, including damage to facial morphology and masticatory function [2, 3]. Oral tissue engineering can not only fix the defect but also restore the function. However, complex tissue types and precise anatomy lead to the challenges of the restoration of the oral and maxillofacial region [4–6]. Nowadays, clinical demands are growing steadily, while the number of products currently available for clinical application is still relatively small [7] (Table 1). In the last 20 years, the number of publications related to oral tissue engineering has rapidly increased (Fig. 1).

**Table 1** Clinical demands of dental implants in 2021

| | Missing teeth | Dental implants |
|---|---|---|
| Globe[7] | 30 billion | 32 million |
| China[8] | 2.20 billion | 4.94 million |

The oral tissue has a wide range of sources, such as hard tissues, soft tissues, the vascular and nervous system, etc. Different tissue injuries might result in defects of different forms. We extracted and summarized the keywords related to oral tissue engineering in the literature. It was found that bone tissue regeneration field has the largest amount of research, followed by soft tissues, and research on nerve and vascular tissue engineering has gradually increased in recent years (Fig. 2).

Biomaterials have played an essential role in tissue engineering. The number of publications in oral tissue engineering and biomaterials has shown the same trend as oral tissue engineering (Fig. 1). Materials like metals [9], bioceramics [10], and polymers[11] are widely utilized due to their stable chemical properties and superior mechanical qualities [12, 13]. But most of these biomaterials are just filling the defect and still far from the normal tissues of the body [14]. In general, the existing tissue repair is still facing challenges such as single and limited repair materials with simple structures, as well as the insufficiency, non-function, and inaccuracy of the repair effect [15–17]. By analyzing the high-frequency materials that appear in publications related to oral tissue engineering AND biomaterials (Fig. 3), we discovered that except for traditional materials like metals and calcium compounds, innovative biomaterials such as hydrogels have become a popular research subject in recent years. Functionalized, personalized, and composited biomaterials become an important topic of research today [18–20].

This narrative review will focus on the significant advancements in biomaterials of oral tissue engineering. The search is conducted in scientific databases, such as Web of Science and PubMed. The search strings for the publication search are the following: 'oral tissue engineering'; 'oral tissue engineering' AND 'biomaterials'. A total of 230 articles were finally selected for reviewing in the literature, and the search strategy is illustrated in Fig. 4. In this review, we provide an overview of (Fig. 5):

(i) The current biomaterials;
(ii) The manufacturing processes;
(iii) The application of oral tissue engineering in clinical therapy and research.
(iv) The role, major challenges, and future directions of oral tissue engineering.

## 2 Main text

### 2.1 Biomaterials of oral tissue engineering

With the emergence of a variety of biomaterials, we can now select the most appropriate material according to the tissue type, structure, and physiological characteristics of the defects in clinic. Although traditional materials such as metals and inorganic materials are still widely used in clinical practice, novel biomaterials like hydrogels and composites combined with bioactive molecules are gradually coming into the public's view. Due to their versatility in morphology and superior tissue regeneration

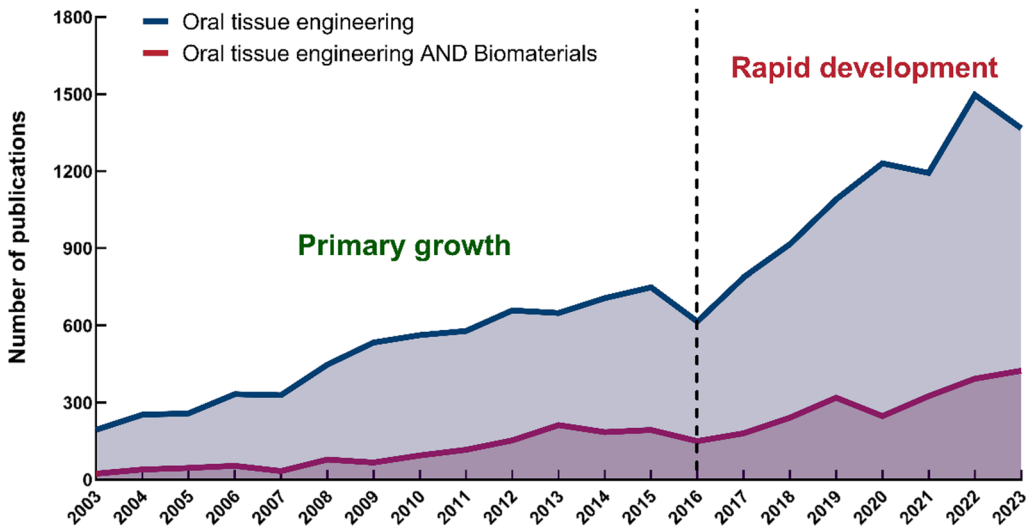



**Fig. 1** The evolution of publications in research field related to oral tissue engineering and biomaterials from 2003 to 2023

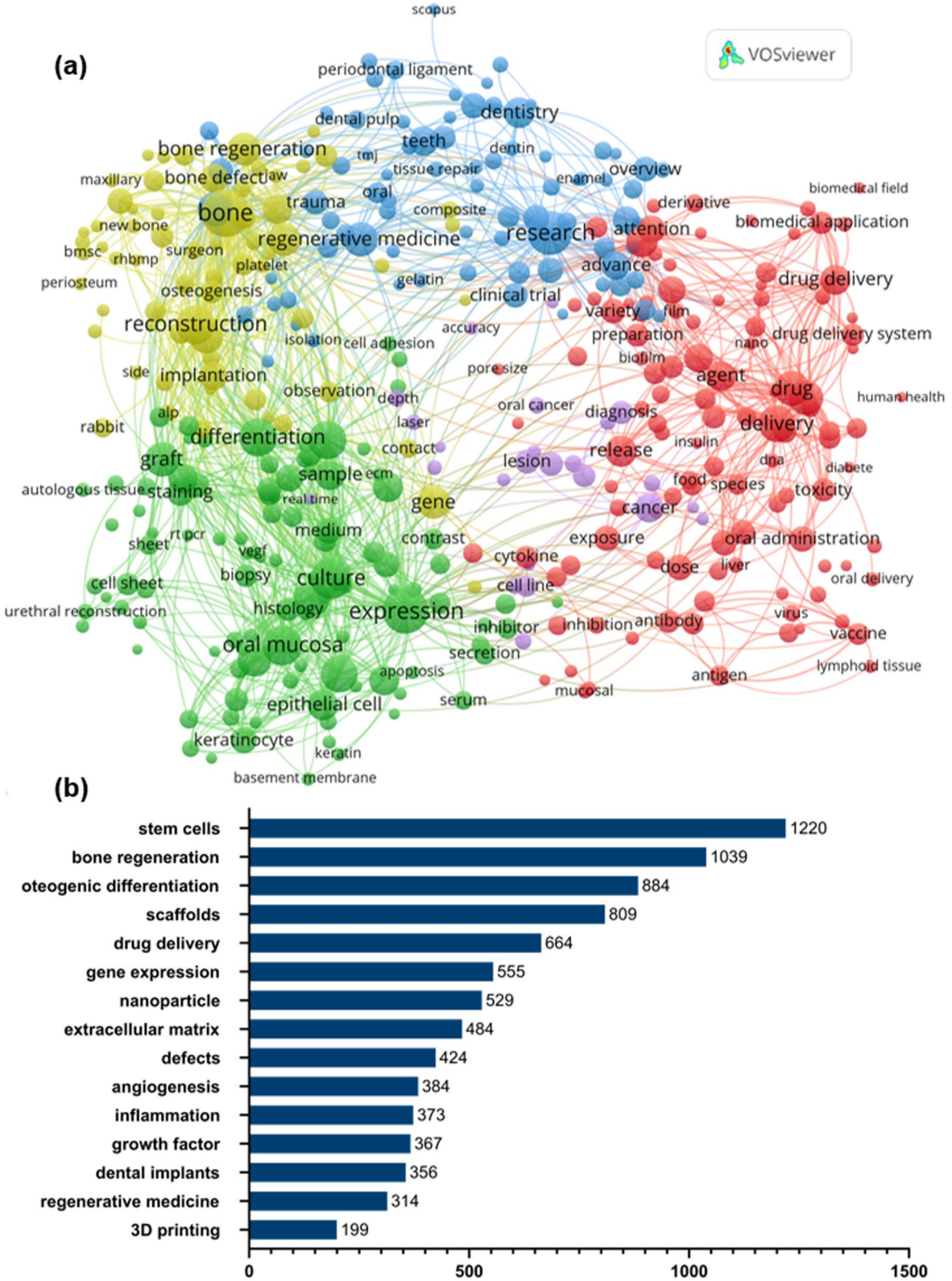



**Fig. 2** **a** Co-occurrence network in research related to oral tissue engineering. **b** The rank of high-frequency keywords in research related to oral tissue engineering

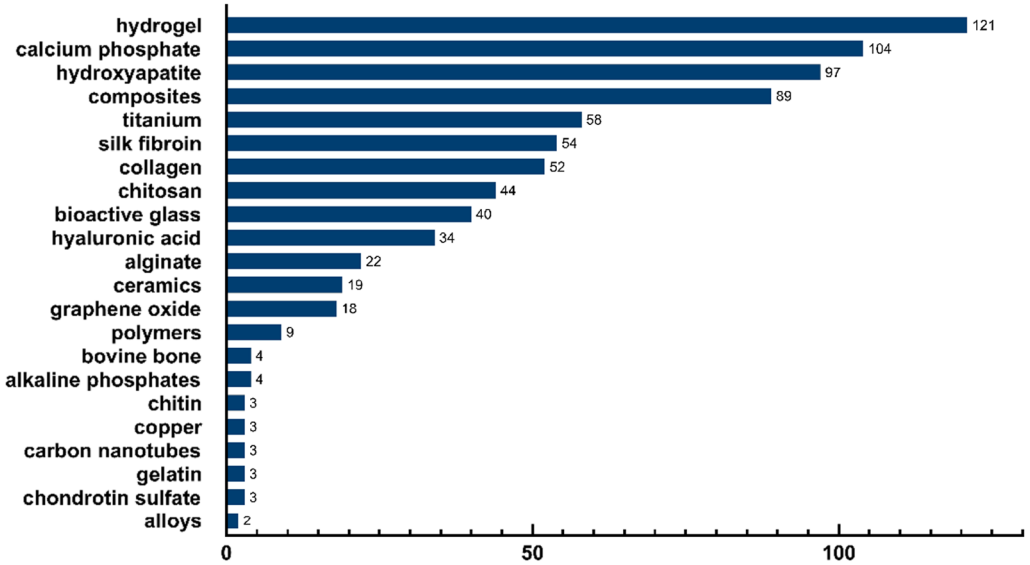



**Fig. 3** The rank of high-frequency biomaterials in research related to oral tissue engineering

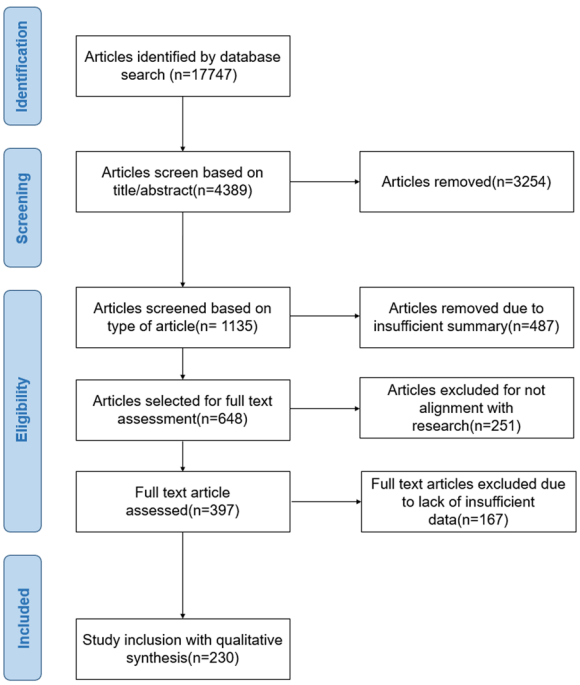



**Fig. 4** Flow diagram for literature search strategy regarding this review

ability, they may lead the future trend of clinical and experimental development (Table 2).

#### *2.1.1 Natural bone grafts*

Natural bone grafts are classified as autologous, allogeneic, and xenogeneic grafts. The current gold standard for all bone grafts is autologous bone grafts. Although autologous bone grafts have superior osteogenic properties, they are not frequently employed in clinical practice because of their restricted origin, high complication rates, and increased operation time. It has been indicated that the complication rate after harvesting autologous bone grafts from the iliac crest is 19.37% [21].

As a result, allografts and xenografts continue to be used more often clinically. Allografts come in three main types, usually taken from cadavers: fresh frozen bone (FFB), freeze-dried bone (FDBA), and decalcified freeze-dried bone (DFDBA). Allografts need to be sterilized and decellularized before clinical application to minimize rejection or disease transmission. These procedures increase the costs of manufacturing and the material resorption rate, resulting in this type of graft being limited to the use of small to medium-sized defects [22].

Xenografts are a cheaper alternative to allografts. They can be derived from bovine, equine, and porcine, and the most widely used one is Bio-Oss® from bovine. Bio-Oss collagen® (90% cancellous bone granules and 10% porcine collagen) is another popular product used in clinic. These materials provide similar support and survival to autologous grafts, but do not have osteogenic properties and should be utilized with caution to minimize the immune response in the affected area. A systematic review compared the bone regeneration potential of implanted autogenous and artificial bone materials after sinus floor elevation. It revealed that autogenous bone grafting led to a higher rate of new bone formation (41.74%) than Bio-Oss® material used alone (8.25%) [23].

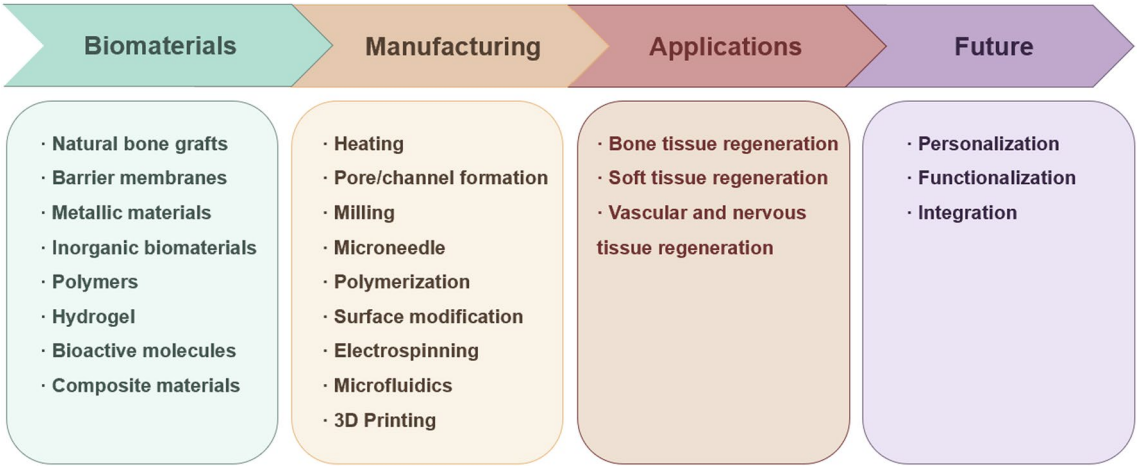



**Fig. 5** Roadmap of sections in the review

Although traditional bone graft materials have outstanding biocompatibility and osteoconductivity, it is challenging to customize them to the patient's specific defects [24]. In addition, shortcomings such as multiple immune reactions, limited access to materials, and complex manufacturing processes make them unable to fully satisfy the existing needs of patients. More research on new biomaterials has thus been proposed.

#### *2.1.2 Barrier membranes*

The definition of barrier membranes for bone augmentation was first proposed by Hurley et al. [25]. Barrier membranes play the role of preventing soft tissue collapse while blocking faster migrating fibroblasts from entering the defect. Therefore, the osteoblasts are allowed to have adequate room to proliferate, thus facilitating bone regeneration [26].

Barrier membranes that have already been put into use include Bio-Gide® (porcine collagen), Heal-all® (bovine collagen), and Millipore™ filters (PTEF and titanium mesh). There is still a need for further improvement as existing membranes suffer from issues like infection, membrane breakdown, and membrane exposure.

Zhu et al. have incorporated magnesium oxide nanoparticles (nMgO) into PLA/gelatin to form a composite membrane via electrospinning to promote bone regeneration of periodontal tissues[27]. Dong et al. successfully fabricated a magnesium oxide nanoparticles (MgONPs)/parathyroid hormone (PTH)-PCL membrane, which could significantly facilitate bone regeneration in periodontitis patients with large-volume bone defects [28]. Jin et al. have used plant polyphenols and LL-37 peptides to modify the fibrous membranes and confirmed that the membranes exhibited outstanding antimicrobial activity and immunoregulation properties [29].

#### *2.1.3 Metallic materials*

Because of high strength and hardness, metallic materials are commonly used in bone repair in the oral and maxillofacial region, serving as mechanical support for structures like soft tissues to avoid tissue displacement and collapse[30]. Despite the widespread use of metallic materials, they have the obvious drawback that particles released by their wear or chemical degradation may interfere with cell metabolism [13].

In the 1920s, stainless steel (SS) was extensively accepted due to its enhanced corrosion resistance and low price. The most popular stainless steel is 316 stainless steel, which is used as reconstruction plates in maxillofacial surgery. The poorer mechanical qualities of these stainless steel alloys, however, led to their progressive replacement with biocompatible and tougher cobalt-chromium (Co-Cr) alloys in the 1930s [31].

Nowadays, the most used metallic materials are titanium and its alloys. In addition to its strong mechanical properties, titanium has exceptional biocompatibility and hydrophilicity, which facilitate the adhesion, proliferation, and differentiation of cells. Titanium is also one of the materials suitable for 3D printing. Due to its softness, aluminum is introduced to titanium to increase the hardness. The most famous alloy is $Ti_6Al_4V$. The major disadvantage of titanium and its alloys is their non-degradability, necessitating subsequent surgery, which prolongs the patients' recovery time and increases their pain.

Another metallic biomaterial with significant potential is magnesium. They can be degraded into completely biocompatible degradation products in vivo [32]. Studies have also demonstrated that magnesium and its alloys promote the expression of osteogenic markers in vitro [24]. Magnesium is rather reactive,

**Table 2** Typical biomaterials of oral tissue engineering

| Category | Common materials | | Main features | Limitations | Representative application | Composite application |
|---|---|---|---|---|---|---|
| Natural bones | Autologous grafts | | Osteoinductive, osteoconductive, osteogenic | Restricted origin, high complication rates, increased operation times | Onlay [65], Shell [66], Flaps [67] | – |
| | Allografts | | Osteoinductive, osteoconductive, osteogenic | High costs, high resorption rate | Bone meal [68], bone block [69] | DFDBA/PRF [68], DFDBA/rifamycin [68], DFDBA/collagen [70] |
| | Xenografts | | Biocompatibility, osteoconductivity | Immune reactions, complex, expensive | Bio-Oss® [71], bone block [72] | Bio-Oss collagen® [71], Lando® [73] |
| Metals | Titanium | | Strong mechanical properties, Biocompatibility, hydrophilicity | Non-degradability | Ti mesh [74], Ti plate [75] | Ti/BMP [76], Ti/Mg2 + [76],Ti/ZrO2 [77] |
| | Magnesium | | Biocompatibility, degradability, osteoconductivity | Reactive | Mg plate [78], Mg coating [76] | Mg/PLGA [22], Mg/HA [13] |
| Inorganic materials | HA | | Biocompatibility, cheap, no tissue rejection | Low mechanical strength | nHA [79], HA scaffold [22], HA cement [24] | nHA/Ti [76], HA/collagen [80], HA/PLGA/collagen [81] |
| | TCP | | Biocompatibility, suitable morphology, controlled pore size | Unsatisfying osteoinductivity | TCP scaffold [82], TCP cement [24] | BCP [24], PCL/TCP/bdECM [83] |
| | Bioactive glass | | Bioactivity, stimulate osteoblast differentiation and hematopoietic reconstitution | Low mechanical strength, fracture toughness | 45S5 Bioglass® [84], PerioGlas® [85], BG scaffold [86] | BG/PCL [22], BG/BMP [87] |
| Polymers | Absorbable | PCL | Slow degradation rate, high mechanical stability | Hydrophobicity, poor cell affinity | PCL scaffold [88], PCL membrane [89], injectable implant [12] | PCL/aspirin/BFP [88], PCL/hydrogel [90] PCL/gelatin/MgO [89], Osteoplug® [12] |
| | | PGA | Hydrophilicity, biocompatibility | Induce inflammatory responses, rapid degradation | PGA sheet [91], PGA scaffold [22], PGA membrane [92] | PLGA [93], PGA/TCP [22] |
| | Non-absorbable | PEEK | High stiffness, small weight, little stress shielding effect, no artifacts | expensive | PEEK prosthesis [94], PEEK plate [95] | PEEK/Ti [96] |
| Hydrogel | Natural | Chitosan | Biocompatibility, antibacterial activity, non-immunogenicity | Low strength, fast degradation, expensive | Drug delivery [97], support provision [76], ECM mimic [76] | Chitosan/Ca [97], chitosan/GO/HA [98], chitosan/gelatin/glycerol phosphate [99] |
| | | Alginate | Bioactivity, non-immunogenicity, low cost, simplicity of gelation | Low strength, fast degradation, soluble | Differentiation induction [85], ECM mimic [24], cell encapsulation [24],drug delivery [100] | Alginate/Lap [101], alginate/GelMA [102],CNF/chitosan/alginate [64] |
| | Synthetic | GelMA | Biocompatibility, minimal immunogenicity, modifiable properties | Low rigidity, limited biodegradation | Cell encapsulation [103], ECM mimic [104], drug delivery [105] | GNT [106], GelMA/TCP/PLA [107], FLASH [108] |
| | | PEG | Biocompatibility, designability | Low mechanical strength | Drug delivery [109], ECM mimic [110] | PEG/PCL [48], PEG/PDA/PUE [111] |
| Bioactive molecules | Drugs | | Antimicrobial and osteogenic properties | Expensive | Antimicrobial agent [112] | Gentamicin/PLGA [112], aspirin/PCL/BFP [88] rifamycin/DFDBA [68] |
| | PRF | | Improved stability, wound healing, and hemostasis | Expensive, instability | Bone augmentation [57], surface modification [76] | PRF/TCP [57], PRF/DFDBA [68], PRF/Ti [76] |
| | Growth factors | | Osteoconductivity, promote angiogenesis and regeneration | Expensive, instability | Bone repair [113] | CGF/Bio-Oss® [76], rhBMP-9/Bioglass® [87], VEGF/collagen [58] |

so there is currently much research into controlling its degradation via fabricating magnesium alloys for in vivo applications.

Additionally, the physicochemical properties of metallic materials can be improved by surface modification such as heat treatment and coating, further enhancing their biocompatibility and stability. Such techniques will be discussed later in 2.2.6 Surface modification.

#### *2.1.4 Inorganic biomaterials*

Inorganic biomaterials imitate the composition of bone tissue for replacement purposes, used clinically as bone fillers to promote new bone production [24]. They can be broadly classified into two categories: calcium compounds and bioactive glass. Inorganic biomaterials can be employed for tissue regeneration in a variety of forms, including meal, sheet, block, paste, coating, or porous scaffolds, with a high degree of plasticity. They are also an ideal material for 3D printing.

Calcium phosphate can be classified into different groups with different stability and/or solubility depending on the ratio of calcium and phosphate: (1) Hydroxyapatite (HA) and α-tricalcium phosphate (α-TCP); (2) BCP, and (3) Dicalcium phosphate dihydrate (DCPD) and β-tricalcium phosphate (β-TCP) [12]. Among them, HA and β-TCP are the best known. HA is a natural mineral component of human bone tissue and can be extracted from animal bone and coral or synthesized artificially [33]. It is often used as a restorative material for large bone defects in the oral and maxillofacial region. β-TCP is another bioceramic material with a more suitable morphology, controlled pore size, and slightly higher biodegradation rate compared with HA [22]. β-TCP products that have been commonly used in oral and maxillofacial applications include IngeniOs™ β-TCP, OSferion™ β-TCP, etc. However, its mechanical strength, degradability, and osteoinductivity are still not satisfying as well. BCP is a bone generation biomaterial that combines the advantages of HA and β-TCP. Products like MasterGraft™ BCP and maxresorb® have been used in clinic.

Bioactive glass (BG), which consists of oxides of silicon, sodium, calcium, phosphorus, and boron, is another popular type of bioceramic. It can exhibit a variety of properties depending on the ratio of the various elements [22]. BG is generally categorized into borate and phosphorate according to its composition, and it can also be distinguished as melt-derived BG and sol-gel BG based on its processing methods [12]. It has also been reported that bioactive glass releases therapeutic ions (mainly silicate and calcium ions) in vivo that stimulate osteoblast differentiation and hematopoietic reconstitution. Additionally, it demonstrates an elastic modulus similar to that of cortical bone, excellent bioactivity, and the capability to regulate cell migration [34].

Depending on the clinical needs, the properties of inorganic materials can be improved by compounding them with polymers or altering their ionic composition in various ways to reduce their brittleness and enhance their osteogenic properties. It will be discussed later in 2.1.8 Composite materials.

#### *2.1.5 Polymers*

Synthetic polymers are industrially manufactured from inorganic components by condensation, ring-opening polymerization (ROP), and direct polymerization. They are categorized as absorbable and non-absorbable polymers. In the field of electrospinning and 3D printing, polymeric materials have also essentially reached maturity.

Absorbable polyesters, represented by aliphatic polyesters, dominate the synthetic polymers, with polycaprolactone (PCL), polylactic acid (PLA), polyglycolic acid (PGA), polyethylene glycol (PEG), etc. being the most common examples. And there are other non-absorbable materials including polytetrafluoroethylene (PTFE), polyethylene (PE), polymethyl methacrylate (PMMA), and polyetheretherketone (PEEK). PCL has an extremely slow degradation rate and high mechanical stability [35], better maintaining the generated bone volume and its contour. However, the hydrophobicity of PCL results in its poor cell affinity and cell-to-surface interactions [36]. In contrast to PCL, PGA has better hydrophilicity. But intracellular degradation of glycolic acid by-products may induce an inflammatory response [22], causing tissue necrosis and scaffold failure. As a result, PGA is often combined with PLA in practice to form a copolymer poly(lactic acid) poly(glycolic acid) (PLGA), compensating for the disadvantages of both materials when used separately.

In recent years, considerable research has been done on a kind of aromatic non-resorbable polymer known as polyetheretherketone (PEEK). It has been reported that unpolished PEEK has a higher surface roughness compared to PMMA and resin matrix composites [37], while the slightly-rough morphology is exactly what is required to promote the growth of both soft and hard tissues. And the surface roughness of polished PEEK can reach the lowest Ra value of $0.009 \pm 0.002$ μm [38]. PEEK can also provide excellent wear resistance. An in vitro study showed that PEEK had a volume loss of only $1.084 \pm 0.109$ $mm^3$ when subjected to 60,000 mastication cycles, which is significantly lower than other materials, such as PMMA[39]. In terms of mechanical properties, it exhibits elastic modulus and tensile characteristics that are comparable to those of cortical bone[40], and little stress shielding effect. Additionally, it has radiation projection

properties and doesn't cause metallic artifacts, helping with postoperative imaging procedures [41]. PEEK is therefore being considered as a possible alternative for metallic materials like titanium in future for large defects in the maxillofacial area. Cheng et al. have applied PEEK to rabbit mandible defect models for bone regeneration and received positive results [42]. Shash et al. have used PEEK to form hybrid prostheses for the restoration of the mastication mechanism of edentulous patients [43]. However, the biological inertness and hydrophobicity of PEEK surface make it difficult for cells and proteins to attach to the material. And due to the lack of antimicrobial properties, the occurrence of infections is prone to lead to the failure of PEEK implants [44]. Currently, clinical attempts have been made to modify PEEK properties. The PEEK materials used nowadays include carbon-reinforced PEEK, nanostructured PEEK, and bioactive PEEK composites [45]. In future, novel peek-based materials prepared by combining multiple modification technologies will become the mainstream of PEEK research. In addition to optimizing mechanical properties and enhancing biocompatibility, postoperative bacteriostatic and immunomodulatory capabilities [46] are constantly being explored.

Additionally, by grafting various functional groups or amino acids into known polymers, the physical and chemical properties of polymers can be altered. For example, Ringot et al. [47] obtained antimicrobial cellulose materials by grafting porphyrin molecules onto cellulose. PCL-PEG-Tyr and PCL-PEG-Ang were synthesized by using tyrosine (Tyr) and angiopep-2 (Ang) as coupling ligands. And it has been proved that this material has excellent sustained-release characteristics [48].

Polymers are widely used as scaffolding materials for soft and hard tissue repair. However, they are currently most frequently used in composite materials with other biomaterials, which will be discussed in 2.1.8 Composite materials later.

#### *2.1.6 Hydrogel*

Hydrogel, a biomaterial with a three-dimensional network structure formed by physical or chemical cross-linking of polymers, is one of the most researched innovative biomaterials in recent years. The hydrogel has excellent adjustability, allowing the change of physicochemical characteristics by environmental factors and modification techniques. Hydrogels are now being used in manufacturing technologies like 3D printing for the repair and regeneration of tissues such as bone, mucosa, skin, blood vessels, and nerves [49]. The physical and chemical characteristics of hydrogel, such as porosity, mechanical strength, and degradation rate, determine its properties [50]. By adjusting the parameters of digital light processing (DLP), there have been researchers able to produce hydrogel products with controllable mechanical strength [51].

Hydrogels can be obtained from two main sources: natural polymers (collagen, gelatin, alginate, etc.) and synthetic ones (PLA, polycaprolactone (PCL), polyethylene glycol (PEG), and methacrylate-based gelatin (GelMA), etc.).

Natural hydrogels are hydrogels derived from natural biological materials. Natural hydrogels resemble natural tissues biologically and chemically since they contain natural elements that make up organisms. Natural hydrogels possess advantages such as bioactivity, non-immunogenicity, and stypticity, but shortcomings such as low strength and fast degradation prevent them from further applications. Because of these drawbacks, they are often combined with synthetic hydrogels.

Synthetic hydrogels stand out for their highly modifiable physical and chemical properties [52]. In addition, they can serve as effective delivery matrices because of the capability of releasing delivery substances consistently and continuously [53]. Therefore, by encapsulating cells, drugs, and growth factors in hydrogels, drug delivery, antibacterial property, vascular regeneration, tissue repair, and electrical conductivity can be achieved [31]. Microchannels can also be constructed in them to diffuse bioparticles and solutions through them, which is a function comparable to the bifurcating vessels [54]. However, poor cell adhesion and limited biodegradation are major disadvantages of synthetic hydrogels as well.

Further experimental research is still required for the structural and functional optimization of hydrogel because the low rigidity and degradation behavior of hydrogels created by 3D bioprinting may result in structural collapse or limiting shape.

#### *2.1.7 Bioactive molecules*

Tissue regeneration involves the joint action of various biological signals. Bioactive molecules can efficiently control the behavior of cell adhesion, proliferation, and migration on materials, significantly improving the tissue regeneration ability of biomaterials [55]. In response to the problem of unsatisfying biological properties of today's biomaterials, scientists have proposed to combine bioactive molecules with materials. Biomaterials can act as carriers to slowly release the carrying substances, accelerating the healing and regeneration of damaged tissues [56].

The success of periodontal tissue regeneration may be hampered by the presence of periodontal pathogens such as Porphyromonas gingivalis and Prevotella intermedia. To encourage periodontal tissue regeneration, it is crucial to control and reduce bacterial contamination

of periodontal defects. Drugs such as azithromycin, tetracycline, and metronidazole benzoate (MET) can enhance the antimicrobial and osteogenic properties of biomaterials, thus preventing the occurrence of complications such as infection.

Platelet-rich fibrin (PRF) is rich in platelets and growth factors that promote the regeneration of periapical bone tissue. Studies have demonstrated advantages for improved stability, wound healing, and hemostasis when PRF and β-tricalcium phosphate are combined [57].

Numerous growth factors precisely control the bone regeneration process in time and space, which has two main phases: vascularization and osteogenic regeneration. Growth factors are now frequently introduced into the materials to enhance osteoconductivity. Bone morphogenetic protein-2 (BMP-2) is the growth factor that currently stimulates the differentiation of stem cells into osteoblasts with maximal activity. Vascular endothelial growth factor (VEGF) can promote angiogenesis after implantation by encouraging cell attachment and intercellular communication when added to the scaffold. In a rabbit mandibular defect model, Liu et al. [58] discovered that BMP-2 and VEGF improved the vascularization and osteogenic regeneration of mineralized collagen porous scaffolds, synergistically promoting the formation of new bones and blood vessels in the mandible. Other bioactive molecules that can be used in combination with biomaterials to promote tissue regeneration in the oral and maxillofacial region include basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF), platelet-derived growth factor (PDGF), enamel matrix derivatives (EMDs), etc. At present, China has approved two kinds of rhBMP-2-carrying biomaterial for clinical use, and the scope of application basically covers all kinds of bone grafting application scenarios [59]. Biomaterials with rhBMP-2 and rhBMP-7 are available in the USA, but they can only be used in maxillary sinus elevation and extraction site preservation in the oral and maxillofacial regionareas [60].

One of the upcoming trends in biomaterials is the use of bioactive molecules, which have more sophisticated design principles. However, the mechanism, the interaction of multiple bioactive molecules, dose design, and the choice of carrier materials are a few of the many significant topics that have not yet been thoroughly studied [61]. The promotion of such materials in clinical practice is also constrained by the high price, immunogenicity, and potential negative effects when used in large dosages. Therefore, there is still a long way to go to study and perfect the properties of bioactive molecules before they finally being put into use on a large scale.

#### *2.1.8 Composite materials*

Since each of the homogenous biomaterials mentioned above has distinct characteristics and particular limitations, scientists have considered combining different materials to promote "synergistic effects" [62]. Composite materials are new repair materials that are constructed by combining two or more materials in a certain ratio. Compared with homogenous materials, the physical, chemical, and biological properties of composite materials are improved, broadening the range of biomaterials and providing a wide variety of options for needs of clinical tissue repair in different application scenarios.

Bone meal can be combined with bioactive molecules to address the problem of lack of osteoinductive and osteogenic properties, increasing its potential for clinical applications. Bioactive molecules that are often combined with bone meal include BMP, VEGF, antibiotics, bone metabolizing drugs, etc. Besides, numerous composite materials with bone meal and collagen as components have been commercialized and, such as Bio-Oss collagen®, Heal-all®, and Lando®.

The main downside of metallic materials is their limited biocompatibility. In order to improve their biological properties, metals can be combined with other materials to create composite materials, by means of surface coatings, etc. The most popular type of coating material is calcium phosphate. The metal/calcium phosphate materials reduce the release of metal ions and enhance their osseointegration as well as regenerative properties.

Existing bioceramics still suffer from high brittleness and difficulty in forming fine structures. Combining them with polymers can maintain their excellent osteogenic function while significantly improving their mechanical properties. At the same time, the disadvantages of polymers' low cellular affinities and immunoinflammatory characteristics are compensated. The fabrication of HA/PLGA composite scaffolds using 3D printing has been investigated [63]. The composite scaffolds show excellent compressibility, elasticity, and high resorptive properties, promoting osteoblast differentiation without an immune response.

As mentioned above, both PLA and PGA suffer from the drawback of quick degradation. In contrast, the degradation time of PLGA, a composite material created by linking the two through an ester bond, may be changed by adjusting the relationship between the two components, considerably enhancing the material's variability in therapeutic applications. Currently, PLGA is widely utilized in dentistry as a bone substitute for regeneration. Moreover, it can be produced in a variety of forms, such as hydrogels, microspheres, blocks, and fibers.

The low rigidity and degrading tendency of hydrogels may lead to structural collapse after implantation into the

target tissue. One of the hottest topics of current research is the combination of hydrogels and carbon nanofibers to create conductive hydrogels. Superior mechanical properties and biocompatibility are shown by the hydrogel/CNF combination [64]. This hydrogel could be utilized for a variety of fields in tissue engineering, particularly nervous tissue engineering.

Although the combination of different materials facilitates the modification of the material, substantial experimental research is still required for the development and application of these materials. To minimize the disadvantages and maximize the advantages of each material, the design of composite materials must be accurate and logical. Additionally, the rather complex manufacturing procedures of composites ask for careful consideration of the interactions between different components so as to prevent harm to the products' effectiveness and safety.

## 2.2 Manufacturing of biomaterials in oral tissue engineering

With the development of interdisciplinary approaches and the advancement of regenerative medicine, biomanufacturing technologies have started to be utilized in oral and maxillofacial surgery in recent years. Among them, the most representative interdisciplinary practice is the integration of material science and biomanufacturing techniques. In addition to traditional technologies that are already in widespread use, emerging biomanufacturing technologies such as microfluidics and 3D printing greatly aided in the production of personalized, functional, and integrated implants [9, 15, 114–116]. Better oral and maxillofacial regeneration is now attainable thanks to the developing manufacturing technologies.

### *2.2.1 Heating*

Calcination is a manufacturing process that modifies the material through the removal of organic matter from it at a high temperature. The removal of immunogenicity and pathogenic bacteria from the material through calcination makes it a popular technique for the manufacture of allografts [117]. Calcined materials retain inorganic mineral components, which provides good biocompatibility while preserving the external structure of the material. However, calcined biomaterials lack active factors that interact with cells since organic components have been removed; hence, they cannot be the most ideal repair material.

Sintering is a process of heat treatment, through which the material powders are compacted, or porous materials are fabricated. It is extensively used for the manufacture of metallic materials. Conventional sintering is energy-consuming and time-consuming, so now we mainly combine it with other advanced technology, such as selective laser sintering (SLS) and selective laser melting (SLM). Kazuya Inoue et al. employed SLM to fabricate personalized titanium mesh for bone augmentation, achieving the regeneration of an ideal alveolar bone shape [118] (Fig. 6a).

Calcination is also an indispensable supplementary method widely utilized in the production of porous bioceramic scaffolds, which is usually carried out after the process of 3D printing nowadays. The porosity, morphology, and mechanical properties of the scaffolds are largely affected by different heating systems. Shao et al. have successfully fabricated customized β-TCP and CSi-Mg10 scaffolds for the preparation of rabbit mandible bone defects using 3D printing and calcination technologies [82].

### *2.2.2 Pore/channel formation*

It is often difficult for nutrients to penetrate inside the large implant, so it's of great importance to form pores or channels to provide space for cells to grow into, absorb nutrients, and carry out metabolic activities. This requires the fabrication of microstructures using a variety of techniques.

Traditional techniques of pore/channel formation include foaming, particle leaching, pore-forming agent methods, and foam impregnation. Incoherent pores inside the scaffolds, uncontrolled structure, and pore size, and poor mechanical properties are all shortcomings of traditional pore/channel production techniques. In addition, structures prepared by traditional techniques of pore/channel formation may contain chemical agent residues and therefore hinder the cell aggregation, making it challenging to carry out biological applications.

Nowadays, 3D printing and microfluidics are frequently used to fabricate pores and channels. Extrusion printing achieves control of pore/channel structures through space adjustments of extruded materials. SLS and DLP can fabricate curved or vein-like channels with high precision. Structures formed by microfluidic systems can be utilized to wrap cells, achieving low material consumption and excellent sensitivity.

### *2.2.3 Milling*

Milling is a manufacturing process based on the gradual removal of material from an initial block of raw material to obtain the final product. Due to its applications in a wide range of materials, excellent accuracy, and high productivity, milling can be used in the mass production of biomaterials, such as dental implants, titanium plates, and titanium nails. However, its drawbacks, including massive material waste and inability to fabricate internal structures, have impeded its further development [119].

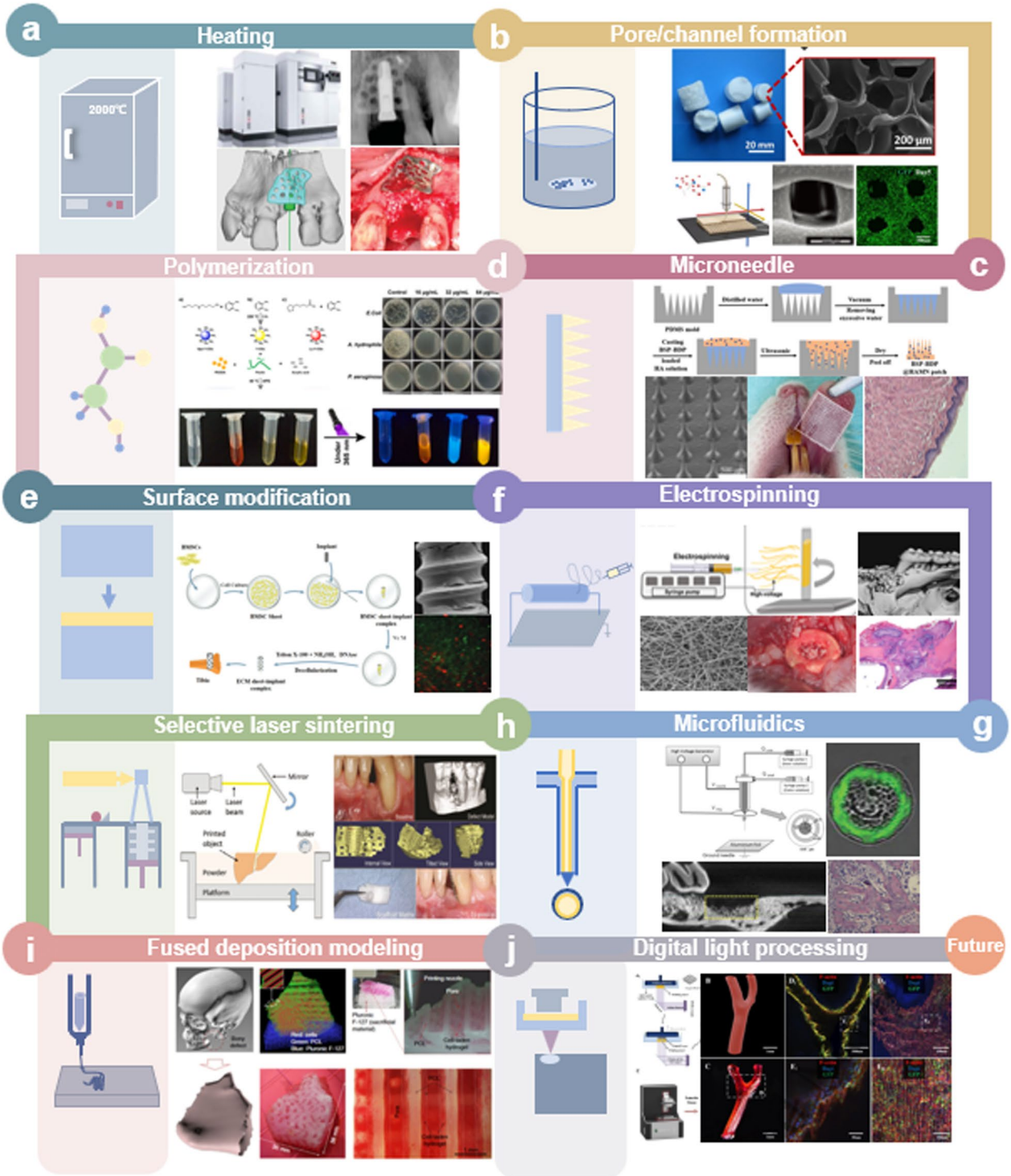



**Fig. 6** The development of manufacturing process and applications

Nowadays, Computer-Aided Design/Computer-Aided Manufacturing (CAD/CAM) has been extensively applied, which is a technology that combines computer technology with milling. In this process, three-dimensional modeling is done using CAD software and then the designed model is input into the subtractive manufacturing machinery for processing [120]. This approach not only enhances the accuracy and the quality

of products with intricate shapes but also significantly improves efficiency. As a traditional method, milling has its obvious advantages of low production costs and simple operation. And it will continue to be used in conjunction with novel technologies, such as computer technology, for the manufacture of biomaterials in future.

#### 2.2.4 Microneedle

Microneedles are microsized needle structures that can penetrate the stratum corneum of the epidermis or mucous membranes for drug delivery. Their typical length ranges from 25 to 2000 μm [121]. The advantages of microneedles being painless, noninvasive, and controllable make them a promising technique for promoting wound healing and tissue regeneration [122]. Currently, technologies including drawing-based methods [123], lithography and etching [124], micromolding [125], and 3D printing [126] are used to prepare microneedles. Among these, micromolding has become the most extensively used method due to its simplicity, inexpensiveness, and reproducibility.

Microneedles are mainly used for drug release by penetration and diffusion, which avoids the need for secondary injection [127]. Antimicrobial, anti-inflammatory, anticancer, tissue regeneration stimulation, and surface anesthesia are five main applications for drug-loaded microneedles. Cargoes loaded on microneedles used in current research include antibiotics, hormones, photosensitizers, cytokines, and anesthetics. Song et al. utilized microneedles as a carrier of metronidazole (Met) for the treatment of periodontal lesions. The results revealed that this method exhibited better efficacy and less toxicity [128]. Guo et al. have prepared hyaluronic acid (HA) microneedle patches containing betamethasone sodium phosphate (BSP) and betamethasone dipropionate (BDP) for better oral ulcer treatment [129] (Fig. 6c). Manimaran et al. demonstrated that indocyanine green (ICG)-loaded microneedle patches could exert a positive effect on photothermal therapy in oral carcinoma [130]. Zhang et al. used GelMA microneedles for the constant release of cytokines, which promotes tissue healing and regeneration in periodontitis patients [131]. Lee et al. discovered that lidocaine-loaded dissolving microneedle could act as a safe and painless local anesthesia method for dental procedures [132].

#### 2.2.5 Polymerization

Polymerization refers to a chemical reaction in which two or more molecules combine to form compounds of higher molecular weight that contain repeating structural units. It's the major process by which we produce synthesis polymeric biomaterials. The traditional polymerization process can be divided into three types: polycondensation, ring-opening polymerization (ROP), and direct polymerization [133].

And nowadays, function groups or peptides are used in polymerization to form new materials with a specific function. These modified materials have numerous applications and can be integrated with techniques like tissue engineering. Carmine Onofrillo et al. prepared a fluorescently labeled sensitive hydrogel (FLASH) by covalently combining GelMA with FITC fluorophores. The fluorescence loss of FLASH can be utilized to track the degradation of the biological scaffold during neonatal cartilage [108].

#### 2.2.6 Surface modification

In terms of biomaterials, we are now facing a series of problems like aseptic loosing resulting from periprosthetic osteolysis [134], and infectious diseases due to the formation of biofilms on the biomaterial surfaces [135], which makes surface modification of biomaterials an essential task. Surface modification enhances the mechanical properties, biocompatibility, and osseointegration performance of biomaterials, which plays an important role in prolonging their life span [136].

*2.2.6.1 Acid etching* The meso-/microporosity and roughness of biomaterial surfaces are crucial to biocompatibility. Acid etching is one of the ways to optimize the roughness and wettability of biomaterial [137], offering an ideal surface for cell adhesion, proliferation, and osteogenic differentiation. Acid etching obtains a complex and irregular topography of the surface using an acid solution like hydrofluoric acid (HF), nitric acid ($HNO_3$), sulfuric acid ($H_2SO_4$), etc. It applied no stress to the biomaterial, so it avoids the problem of material delaminating [138]. However, undesirable chemical reactions may take place during the process of acid etching, which is its main disadvantage [139].

*2.2.6.2 Sandblasting* Sandblasting is another additive modification in common use. It achieves an increase in the roughness of biomaterials by applying ceramic particles (alumina ($Al_2O_3$), titania ($TiO_2$), and silicon dioxide ($SiO_2$)) and compressed air. There are several factors influencing the roughness of the surface, namely sizes, shapes, and kinetic energy of blasting material particles, and the latter is determined by the density, volume, and velocity of the particles [140]. The ceramic particles are supposed to possess high stability, biocompatibility, and non-toxicity, since it may be difficult for the ceramic particles to be removed [141].

*2.2.6.3 Coatings* Coatings are one of the most widely utilized additive modifications, which means creating an

extra structure on the biomaterial surfaces, in order to improve its surface properties such as corrosion resistance [142]. On the one hand, coatings can be divided into inorganic coatings, composite coatings, and organic coatings according to the types of coating materials. On the other hand, surface treatment techniques include electropolishing and anodizing processes, plasma-assisted anodizing (PEO), and sol–gel technique [13].

Coatings based on inorganic materials such as calcium phosphate (CaP) are the first developed since the similarities to natural bone enable them to promote osseointegration between the biomaterial and host tissue [142]. Then ion coatings are frequently employed for various applications to enhance biocompatibility and bioactivity of materials. Gong et al. demonstrated that surface modification using divalent main group element ions ($Mg^{2+}$, $Ca^{2+}$, $Sr^{2+}$, $Ba^{2+}$) can upregulate the adhesion, proliferation, and osteogenic differentiation of bone marrow mesenchymal stem cells. Among them, Sr-modified implants also down-regulate osteoclastogenesis, inflammatory response, and fibrosis [143]. There are other coatings that are connected to the antibacterial properties of materials. Vu el at. has deposited ZnO-, $SiO_2$-, and $Ag_2O$-doped HA coating (ZnSiAg-HA) on the Ti implants and demonstrated that the silver ions that were released from the coating can provide antibacterial activities against Escherichia coli and Staphylococcus aureus [144]. The development of coatings has gradually shifted from changes in coating compositions to changes in coating structures. Huang et al. analyzed the properties pf coating fabricated by co-deposition of $Fe_3O_4$ nanoparticles and PDA on the surface of 3D-printed porous Ti scaffolds. They observed that the coating can support cell attachment, proliferation, and osteogenic differentiation of BMDSCs in vivo [145].

*2.2.6.4 Biological modification* The interaction between tissues and materials has been the focus of biomaterials research and development, and the connection of cells to the material surface is particularly important. Materials should be employed to simulate the morphology of natural tissue structures since the properties of the material surface greatly influence the biological activity of the cells. Bioactive molecules play a fundamental role in regulating cell and tissue differentiation and remodeling, so biological modification has become a representative research direction for surface modification [140].

Biological modification is a method of incorporating bioactive molecules such as peptides, enzymes, cell sheets, or live cells into biomaterials to modify their biochemical properties and biological responses. This approach allows control of the implant-tissue interface and thus determines the repair condition of the tissues. Fu et al. completed the biological modification of titanium using an osteoblast binding motif, P15 peptide. They discovered that the modified surface may provide improved osseointegration outcomes [146]. Gong et al. synthesized a multifunction chimeric peptide from fragments of hBD3 and RGD to modify the titanium surface. According to the results, the chimeric peptide-modified titanium can prevent the formation of biofilm by inhibiting the early attachment of bacteria [147]. Feng et al. combined rat bone marrow mesenchymal stem cell (BMSC)-derived ECM sheets with sandblasted, large-size, acid-etched implants to create ECM sheet-implant complexes. The results showed that this material showed significantly improved cell adhesion, proliferation, and osseointegration [148] (Fig. 6e) In a study of Li et al. injectable photo-cross-linkable GelMA/silk fibroin glycidyl methacrylate (SilMA) hydrogels encapsulating gingival tissue-derived MSCs (GMSCs) are developed to modify the surface of implants, which may act as a potential strategy for clinical application in peri-implant epithelium (PIE) integration [149].

#### *2.2.7 Electrospinning*

Electrospinning is a manufacturing technology to produce nanofibers by jetting a polymer solution in a strong electric field. It can be applied as an effective method for the preparation of biodegradable membranes and scaffolds with porous microstructures [150]. Such structures can be functionalized to carry inorganic substances, bioactive molecules or drugs, and have the potential to mimic the natural extracellular matrix (ECM) [151]. The major disadvantages of electrospinning are relatively low efficiency and high pollution.

Mahmoud et al. fabricated a nanoscale β-TCP-laden GelMA/PCL-TCP photocrosslinkable composite fibrous membranes using electrospinning and the membranes significantly enhanced bone regeneration [152]. Gan et al. designed a 3D PCL/PLA/carbon nanotubes (CNTs) disk scaffold that resembled the anatomy structure of native disks. According to their research, this scaffold could provide a promising clinical solution to TMD ailments [153]. Ren et al. employed electrospinning to produce a fibrous membrane containing cerium oxide nanoparticles ($CeO_2$-NPs) and proved its improved mechanical strength as well as osteogenic properties [154]. Liu et al. reported a one-step treatment of periodontitis based on a core-shell nanofiber membrane constructed by electrospinning. The membrane exhibited a time-programmed release behavior of bioactive molecules, which is essential for osteogenic induction [155]. Ji et al. have developed core–shell poly lactic-co-glycolic acid (PLGA)/gelatin nanofibers, which can sequentially release substance P

(SP) and alendronate (ALN), thus facilitating immediate implant osseointegration [156].

#### 2.2.8 Microfluidics

Microfluidics refers to the precise control of minute amounts of liquid on tiny structures, which can be used for the preparation of microstructured materials. Its principles are as follows. Two immiscible fluids enter and meet from different ports of a microchannel at a certain flow rate. By applying external forces like voltage, air pressure, and magnetic fields, or by regulating the microchannel structure and the fluid flow rate, the formation of microdroplets is induced [157]. Diverse 3D constructions with different structures and material components can be realized by constructing or stacking droplets and fibers [158]. It's also possible to fabricate biocompatible cellular structures by encapsulating or loading cells in droplets [158]. Microfluidics possesses some superior advantages over conventional manufacturing techniques due to the small scale, including less material consumption, high sensitivity, and high resolution [159].

Chang et al. use microfluidic system to prepare poly-(D, L-lactide) and poly-(D, L-lactide-co-glycolide) (PDLLA-PLGA) microspheres encapsulating PDGF and simvastatin, which were then filled into maxillary periodontal defects of rats. It was shown that the microspheres significantly accelerated the regeneration of the periodontal apparatus [160] (Fig. 6g). In a study by Pierfrancesco Pagella et al., trigeminal ganglia (TG) and teeth can achieve long-term survival when co-cultured in a microfluidic system. The results also showed that TG maintained the same innervation pattern as in vivo [161]. Zhang et al. prepared injectable hybrid RGD-alginate/laponite (RGD-Alg/Lap) hydrogel microspheres, co-encapsulating human dental pulp stem cells (hDPSCs) and VEGF according to microfluidic principles. And the microspheres exhibited excellent abilities to facilitate the regeneration of pulp-like tissues as well as the formation of new microvessels [101]. Liang et al. successfully fabricated GelMA-alginate core-shell microcapsules to co-encapsulate hDPSCs and human umbilical vein endothelial cells (HUVECs) based on microfluidic technology. This method is promising for functional vascularized endodontic regeneration [102]. Zheng et al. cultured hDPSCs on hydrogel microspheres incorporated with decellularized dental pulp matrix-derived bioactive factors. The hDPSCs-microcarriers achieved the regeneration of pulp-dentin complex in vivo [162].

#### 2.2.9 Three-dimensional (3D) printing

Three-dimensional (3D) printing is a rapid-developing technique to form a structure based on a designed digital model. According to the "addition principle", the printing system cuts the three-dimensional image data into two-dimensional thin layers, and materials are superimposed layer by layer to achieve the final product [163]. A vast variety of biomaterials can be produced by 3D printing, such as metals, bioceramics, polymers, and composite materials.

*2.2.9.1 Selective laser sintering (SLS)* Selective laser sintering(SLS) is a rapid solid freeform manufacturing technology, using a laser to fuse or melt material powders to produce solid models or objects. The material powders of each layer are laser scanned based on the 2D data to cause the material particles to cure and sinter. And the layers are then stacked and sintered to create a 3D structured object [164]. SLS is known for the advantages of no toxic solvent needs, excellent mechanical properties, and high utilization ratio [31]. The disadvantage is that manufactured products are easy to spheroidize, resulting in a decrease in product quality [165].

G. Rasperini et al. designed a personalized PCL scaffold fabricated by SLS for the repair of periodontal bone defects in patients with aggressive periodontitis. It revealed that the scaffold had been in situ for a year with no signs of chronic inflammation or dehiscence. [166] (Fig. 6h). Yoav Leiser et al. fabricated a personalized titanium mandible using SLS to reconstruct a nearly total avulsed mandible resulting from a gunshot. Postoperative examinations showed aesthetically as well as functionally excellent outcomes [167]. Francesco Grecchi et al. reported a customized prosthesis used to repair the mandible defect caused by subtotal mandibular resection, which effectively restored the masticatory function of the patient [168].

*2.2.9.2 Fused deposition modeling (FDM)* FDM is an extrusion printing technique based on the thermoplastic nature of the material. At the nozzle, the thermoplastic material is thermally melted into a semi-liquid state and then extruded. In order to form the desired three-dimensional structure, the nozzle moves horizontally to create a two-dimensional geometry while the platform is moved vertically to cure the material layer by layer [164]. By changing the printing speed, layer thickness, and printing direction during the manufacturing process, the quality of the extruded material can be altered [169]. The fast production speed, low cost of this technology, and no need for expensive laser sintering equipment are its main benefits [170].

Initially, FDM technology produced mostly single materials without cell-laden capability. But as the technology progressed, the printing of composite materials as well as cell-laden materials gradually came to the attention of researchers. Shao et al. used FDM to print

β-TCP and CSi-Mg10 scaffolds for mandible defects and then compared their physiochemical properties as well as osteogenic capability [86]. SE EUN KIM et al. have successfully repaired a maxillary bone defect in a dog following tumor removal based on FDM printed PCL/β-TCP composite scaffolds [171]. Ye et al. employed a custom 3D printing system based on FDM to print polyion complexes (PIC) scaffolds. The scaffolds were then used for hierarchical vascularized engineered bone for ensuring better reconstruction of mandible function [172]. Byoung Soo Kim et al. have presented a novel bioprinting method based on FDM, introducing PCL as a protective layer to solve the problem of cell death caused by high temperature while printing [173]. Hyun-Wook Kang et al. developed an FDM-based integrated tissue organ printer (ITOP) that successfully printed a completed structure of human mandibles. It has been confirmed that the printing process would not adversely affect cell viability [174] (Fig. 6i).

Nowadays, a relatively mature system has been developed for the printing of composite materials with complex structures. However, the printing system still suffers from slow printing speed and possible cell death during the printing process. In order to solve the existing problems, scientists need to consider various approaches to shorten the printing time while improving accuracy. At the same time, the combination of FDM with biotechnology such as cell culture technology is essential to achieve true bioprinting.

*2.2.9.3 Digital light processing (DLP)* Digital light processing (DLP) is a manufacturing technology that makes use of the light-curing properties of materials for layer-by-layer printing. The construction of the material's three-dimensional structure is achieved by the curing of the projection light source one plane at a time and the vertical movement of the platform [175]. Notably, DLP uses a nozzle-free printing technology, making it one of the highest-resolution printing methods available with high speed [176]. DLP printing has high demands on the printability, biocompatibility, and mechanical properties of bioinks [177], which is the main challenge.

The research of DLP has evolved from single-material to multiple-material printing and from printing without cells to bioprinting. Xu et al. have developed a novel bioactive glass based on apatite and wollastonite, and printed scaffolds using DLP system for the repair of rabbit mandibles [86]. Ju-Won Kim et al. evaluated the bone regenerative capability of customizable HA/TCP composite scaffolds produced by DLP system. Using DLP system can obviously improve the accuracy of the printed scaffolds [178]. Sun et al. proposed a digital light processing bioprinting (DLBP) method to produce customized hydrogels of tissues and organs with complex shapes and controlled mechanical properties using GelMA bioinks. This printing technique has a very high printing resolution and is suitable for creating fine structures of tissues, achieving the functionalization of the biomaterials. Structures such as branching blood vessels, skin, and ears can all be printed in this way [51] (Fig. 6j). In the research of Zhou et al., an innovative method to print functional living skin (FLS) using GelMA/HA-NB/LAP bioink and DLP technology is proposed. FLS has interconnected microchannels that effectively neovascularize and encourage skin regeneration [179]. Xie et al. achieved rapid bone repair in 4 weeks using bone BMSC-loaded hydrogel microspheres (MSs) printed by DLP system. The printed BMSC-loaded MSs showed superior chondrogenic efficiency [180].

### 2.3 Applications of biomaterials in oral tissue engineering

The oral and maxillofacial region has three histological types: hard tissues, soft tissues, the vascular and nervous system. Injuries in different tissues and with different causes might result in defects of different forms, thus requiring implants of varying properties. In terms of hard tissues, how to find materials with matched mechanical strength to complex tissues is still a big challenge. Soft tissue abnormalities are typically repaired using neighboring flaps, but this method has problems with postoperative adhesions and shrinkage that are challenging to resolve [181–183]. Damage to the vascular and nervous system can cause tissue contractures and necrosis, gangrene, numbness, and movement disorders [184, 185]. It's urgent that we explore ideal biomaterials to suit the complicated situation in oral tissue engineering.

#### *2.3.1 Bone tissue regeneration*

Bone tissue is essential for sustaining the hematological system, supporting and safeguarding vital organs, and serving a variety of other crucial physiological and structural functions in the body. Bone abnormalities are common problems that may occur as a result of trauma, infection, tumors, congenital diseases, or even just aging. Therefore, biomaterials are required to repair the destroyed tissue and guarantee a secure bond between the materials and the host bone.

*2.3.1.1 Periapical bone defects* Periapical periodontitis and periapical cysts are the main causes of periapical bone defects. Periapical periodontitis often affects periapical alveolar bones and apical cementum, and periapical cysts usually form in the apical part of a dead pulp tooth. The dead space left after apical surgery is generally the primary cause of delayed wound healing; therefore, bone filling of the surgical wound following periapical surgery is

a crucial stage in periapical repair. The current treatment method for periapical bone defects is mainly the filling or injection of materials following flap surgery.

The first commercial products used for the treatment of periapical bone defects are mainly inorganic materials, such as Bio-Oss®, Lando®, and Gegreen®. Then there appeared composite materials like Bio-Oss collagen® and Heal-all®.

In a clinical study by Charudatta Naik et al., PCL scaffolds were used to repair the bone defect after the enucleation of periapical cysts. They discovered that PCL scaffolds had the potential for bone regeneration, but they still exhibited a marked tendency for dehiscence [186]. Zhang et al. synthesized a Zn/Cu-substituted dicalcium silicate (C2S) bone cement by sol-gel technique. In comparison to pure C2S cement, this multifunctional bone cement demonstrated more significant osteogenic, antibacterial, and appropriate biodegradation abilities [187]. Li et al. investigated the anti-inflammatory and osteogenic properties of chitosan-coated calcium hydroxide microcapsules (CS-EC@Ca microcapsules). In the mandibular defect of the AP rabbit model, CS-EC@Ca microcapsules significantly reduced inflammation and promoted osteogenesis in an inflammatory environment [97]. Cong Li et al. prepared antimicrobial peptide KSL-W-loaded PLGA slow-release microspheres (KSL-W@PLGA) using cryogenic deposition 3D printing technology. According to the findings, it demonstrated noticeably strong antibacterial performance against Enterococcus faecalis and Porphyromonas gingivalis [188] (Fig. 7a).

*2.3.1.2 Bone augmentation* Bone augmentation is frequently performed to address the lack of bone volume in the alveolar bone, preparing for subsequent treatments such as implants. It has increasingly been carried out using guided bone regeneration (GBR), a technique that combines biological membranes and bone grafts, mostly by filling the defect with bone meal and coating the surface with a membrane [189]. Its application scenarios include horizontal or vertical bone defects caused by one or more teeth loss and periodontitis.

For minor bone defects, particle materials are frequently utilized as bone substitutes, similar to periapical bone defects. It becomes increasingly necessary to use block materials for the repair as the size of the bone defect increases. For severe vertical bone defects, materials that restore the vertical height of the bone, such as scaffolds are used. In a randomized clinical trial by Hussein S. Basma et al., small particles (SP) and large particles (LP) of corticocancellous bone allografts are used for bone augmentation, and their effects are compared. According to the findings, there was a trend for greater ridge width gain when LP was used [190]. Claudia Rode et al. synthesized a biodegradable composite material made of an isocyanate-terminated co-oligoester prepolymer and precipitated calcium carbonated spherulites. They discovered that when material blocks were used in mandible defects of pigs, the material showed outstanding biocompatibility [191]. Ho Lee et al. reported the use of a polycaprolactone/bioactive glass scaffold fabricated by 3D printing to perform bone augmentation in a patient's mandible. This procedure saves the trouble of scaffold trimming during the surgery [192] (Fig. 7b).

Biological membranes can be divided into three categories: cell sheet membranes, decellularized membranes, and synthetic membranes. Synthetic biofilms can be subcategorized into monolayer membranes and multilayer membranes [193]. You et al. used 4D printing technology to prepare multi-reactive bilayer morphing membranes consisting of shape memory polymer (SMP) layers and hydrogel layers. The membranes have the ability to digitally adjust their 3D geometry to match the specific bone shape in clinical [194]. Li et al. created a digital titanium mesh that can guide bone augmentation based on the position of the prosthesis. The procedure time, patient discomfort, and the risk of an infection in the surgical area were all greatly decreased by this approach. Compared to resorbable membranes, digital titanium mesh is more effective at preserving the osteogenic space and promoting bone regeneration [195] (Fig. 7e). Mohammad Ali Ghavimi et al. developed an asymmetric GBR membrane for the sustained release and local delivery of curcumin and aspirin. In the dog's jaw bone defect model, the membrane presented excellent antibacterial activities and bone regeneration effects [196].

*2.3.1.3 Cysts of the jaws* The jaws are the most preferred site for cysts in the human skeleton due to their specific anatomy and intricate embryologic development. It is essential to expedite the repair of the bone defect following jaw cyst surgery because it affects the morphology and quality of the jaw bone and raises the risk of future infection.

Different from periapical bone defects, defects caused by cysts of the jaws require bone substitutes with better mechanical strength and support effect. Since cyst bone defects are often of irregular shapes and contours, personalized substitute manufacturing is also a crucial topic of research. In clinical practice, bone cement, block, or scaffold materials are often filled into the defect area depending on the size of the bone defect. Alexandra Dreanca et al. prepared a novel graphene dental cement to repair mandible bone defects in rats. They demonstrated that the graphene materials had good biocompatibility and could stand as promising candidates for future bone

cement [197]. Deepak Gupta et al. fabricated a personalized resorbable PCL core framework by combining 3D printing and freeze-drying techniques. And a hydrogel coating made from a complex of Gel, CMC, and HA was implemented on the scaffold. This scaffold has significantly higher mechanical strength than natural hydrogel scaffolds, which compensates for the shortcomings of existing hydrogel materials [198]. Ye et al. fabricated a hierarchical vascularized engineered bone (HVEB) for the repair of mandibular defects based on polyion complexes (PIC) scaffolds, gradient carrier hydrogels, and seed cells by extrusion 3D printing. This repair technique showed high efficacy in vascularization and bone regeneration while simulating the spatiotemporal structure of intra-membrane ossification [172] (Fig. 7d).

Bone defects resulting from jaw cysts can sometimes be accompanied by pathological fractures. A fixation plate might also be used if the bone of the lesion area is thin. Gabriel Armencea et al. evaluated the microscopic structure of soft tissue and qualified the metallic particles after titanium plate implantation in jaw surgeries. Their findings claimed that although there were no signs of acute inflammation, de-coloration of the periosteum and migration of metallic particles could be observed, which might lead to tissue irritation and hardware loosening over time [199]. Tolunay Avci et al. compared the performance of the Cfr-PEEK plate and titanium plate in the treatment of mandibular angulus fractures. They came to the conclusion that Cfr-PEEK plates could be a better choice for the repair treatment [200]. Atul Singh et al. have used Inion CPS® resorbable plates in the fixation of mandible fractures. They noted that resorbable plates could be an essential tool owing to the benefits such as biodegradability and biocompatibility [201].

*2.3.1.4 Jaw tumors* Jaw tumors are benign and malignant tumors that mostly develop in the maxilla, mandible, and surrounding tissues. The vast invasive range of tumors and the complicated anatomical relationships around the jaw bone make jaw tumors prone to recurrence after surgery. Inadequate treatment may also result in malunion and functional disorders.

The basic principles of treatment for bone defects caused by jaw tumors are fixation and reconstruction. Usually, the treatment is more focused on the restoration of the shapes of large defects. Scientists are trying to apply manufacturing methods such as 3D printing to fabricate personalized bone implants to fit varying shapes of defects. P.S. Unnikrishnan et al. implanted nanocomposite fiber scaffolds (poly-L-lactic acid yarn-CSF reinforced silica nanohydroxyapatite gelatin) in a porcine mandibular defect model. The results showed that the scaffolds promoted high-quality bone formation in the mandibular defect, leading to successful osseointegration [202]. Xu et al. prepared a personalized bioactive glass–ceramic (AP40mod) scaffold using the DLP system and performed inoculation of endothelial progenitor cells (EPCs) and mesenchymal stem cells (BMSCs) on the scaffold. The results showed that the scaffold contributed greatly to osteogenesis, collagen maturation, and angiogenesis in the defect area [86]. Chen et al. have developed a Chinese customized total temporomandibular joint prostheses designed and manufactured using 3D printing technologies such as EBM and SLA. According to postoperative evaluation, such prosthesis could produce good functional improvement as well as high implantation precision. And it is highly suitable for Chinese anatomical features, possessing a broad clinical application value [203] (Fig. 7e).

In the future, the hotspot of research in tumor bone defects may shift to strategies for the elimination of tumor cells and prevention of recurrence. Yan Wu et al. developed a 3D-printed calcium phosphate cement (CPC) scaffold with an anticancer drug 5-fluorouracil (5-FU) coating. The scaffold acted as not only a personalized bone graft material, but also a drug delivery system for the treatment of bone tumors [204]. It has been demonstrated graphene oxide (GO) is a photothermal substance that can be utilized in tumor treatment. A high-temperature localized area within the tumor is produced by GO, which efficiently transforms light energy into heat energy and aids in tumor ablation [205]. Lai et al. have succeeded in preparing graphene oxide/hyaluronic acid/chitosan (GO/HA/CS) composite hydrogel scaffolds using 3D printing technology [98].

*2.3.1.5 Trauma* While firearm injuries are the main cause during wartime, traffic accidents are the major cause of maxillofacial traumas in modern times due to the swift growth of the automobile and transportation industries.

In comparison to long bones, jaw defects caused by trauma are more prone to infection due to the abundant blood circulation and complicated structure. Therefore, there is an urgent need to develop biomaterials with excellent repair and reconstruction functions as well as effective antibacterial properties to treat trauma-induced maxillofacial bone defects. Zhang et al. prepared a β-TCP nanoparticle/PLGA/dichloromethane scaffold containing chlorhexidine (CHX) loaded graphene oxide (GO) nanosheets and osteogenic peptide . It has a controlled two-stage drug release to achieve antimicrobial, infection recurrence prevention, and osteogenic treatment during infected bone reconstruction [206] (Fig. 7f). Nie et al. developed a personalized GelMA/β-TCP/sodium alginate /MXene scaffold with excellent photothermal antibacterial and osteogenic abilities by 3D printing. The

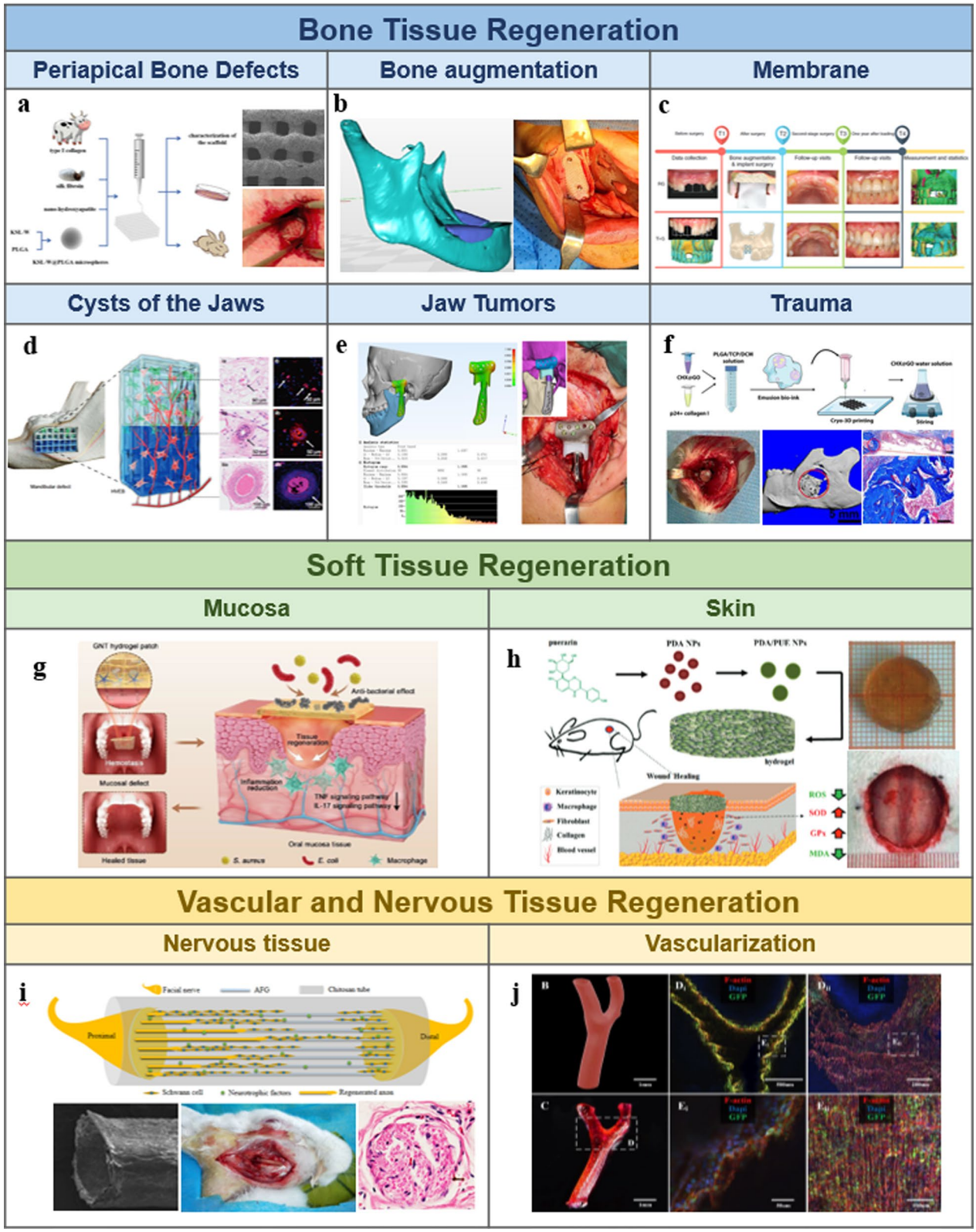



**Fig. 7** Typical applications of biomaterials in oral tissue engineering

scaffold was able to play synergistic roles in antibacterial and osteogenic effects, accelerating the healing of infection and bone regeneration [207].

Trauma-induced bone defects are often irregular and structurally complex, which increases the difficulty of their repair. Among them, the repair of condylar injuries remains a major challenge for clinical work. Since the condyle is responsible for physiological functions such as mastication and speech, repair materials of high performance are required. The research of condylar repair methods has advanced from morphological restoration to taking into account functional reconstruction. And the repairing range also gradually evolved from small-scale defect repair to total temporomandibular joint (TMJ) reconstruction. Wang et al. prepared a bilayer composite scaffold using thiolated hyaluronic acid (HA-SH)/type I collagen (Col I) blend hydrogel, BCP, rabbit bone mesenchymal stem cells (rBMSCs), and chondrocytes. The scaffold could simulate the structure of condylar osteochondral defects, achieving condylar cartilage regeneration [208]. Chen et al. have used 3D printing to develop a Chinese customized TMJ prosthesis. The prosthesis is composed of a Co-Cr–Mo condylar head, $Ti_6Al_4V$ ramus component, and ultra-high molecular weight polyethylene (UHMWPE) fossa component, showing excellent functional improvement after the surgery[203]. Zou et al. fabricated an artificial TMJ prosthesis for lateral pterygoid muscle (LPM) attachment with a 3D-printed titanium alloy. The prosthesis provided the possibility for the growth and attachment of muscles, solving the problem of motor dysfunction caused by LPM attachment loss [209].

#### *2.3.2 Soft tissue regeneration*

*2.3.2.1 Mucosa* The mucosa can be divided into epithelium and lamina propria. Ulcers and wounds are two main types of mucosa defects in maxillofacial regions. Ulcer, the most common oral mucosa disorder, is a round- or oval-shaped defect resulting from necrotic detachment of the mucosa surface layer. As the mechanisms of ulcers are still unclear, symptomatic treatment is recommended as a first-line treatment [125]. As for oral mucosal wounds, they usually can't be sutured or pushed together directly after lesion resections. Therefore, neighboring muscle flap transfers and free skin or mucosal slices were frequently used for repairs. However, the complexity of the surgical procedure lengthens the procedure thus raising the danger of this repair method.

The main method of ulcer treatment is local medication, which can be subdivided into local injection and transmucosal administration. Forms of transmucosal administration include gels [210], ointments [211], mouthwashes [125], and patches [212]. However, the barrier effect of the oral mucosal epithelium and the dilution effect of saliva can negatively influence the efficiency of traditional drug delivery. Currently, microneedles have become a hot topic of research for steady drug release in ulcer treatment. Guo et al. fabricated a dissolvable microneedle patch loaded with BSP-BDP with HA, which significantly promoted the healing of oral ulcers [129]. Wang et al. constructed a multidrug microneedle patch containing dexamethasone acetate, vitamin C, and tetracaine hydrochloride. The patch enhanced not only anti-inflammatory effect of dexamethasone, but also the pro-proliferation effect of vitamin C [125]. In the research of Li et al., a double-layer microneedle patch composed of HA tip part and the polyvinylpyrrolidone (PVP) base part is produced to further promote the efficacy of drug release [213].

Traditional mucosal repair was more focused on the restoration based on the morphological structure of the tissue. Commercial products that have been used in clinic include Mucograft® (porcine collagen), Bonanga® (Type I collagen from bovine Achilles tendon), and Matriderm®. Nowadays, mucosal repair utilizing cell-laden biomaterials is the main area of focus. Tang et al. fabricated a biomimetic electrospun matrix derived from a solution of filamentous nanofibers. Evaluation in a rat buccal mucosa repair model showed that the filamentous protein matrix had better wound healing, improved wound contraction inhibition, and reduced local immune incompatibility [214]. Zhu et al. developed low-swelling viscous hydrogels (GNT) with superior physicochemical properties using GelMA, nanoclay, and tannic acid (TA). The results showed that GNT hydrogels possess strong hemostatic properties and excellent antibacterial and anti-inflammatory effects to accelerate the repair of defective mucosa [106] (Fig. 7g). Maryam Mardani et al. prepared adipose tissue-derived stem cells (ADSCs)-seeded curcumin/collagen scaffolds to treat rat buccal mucosa. It's demonstrated that the scaffolds could better help with the healing of mucosa defects [215]. Zhou et al. constructed vascularized oral mucosa-like structures with ACVM-0.25% HLC-I scaffold, human gingival fibroblasts (HGFs), human gingival epithelial cells (HGECs), and vascular endothelial-like cells (VEC-like cells). The scaffold exhibited excellent capability in promoting repair of mucosa [216].

*2.3.2.2 Skin* The skin is composed of epidermis and dermis, containing appendages such as hair, sebaceous gland, and sweat gland. The high quality and quick repair of skin defects remain a significant challenge because of the limitations of autologous tissues, a scarcity of skin donors, and damage to the skin graft area [217].

Early commercial products used for the treatment of skin defects were mainly acellular artificial skin, usually prepared by chemical synthesis or decellularization, such as Alloderm® (allogeneic decellularized dermal matrix of human), Biobrane® (Type I collagen of porcine), and Integra® (polysiloxane, gum sulfuric acid, chondroitin-6 sulfate). Later developed products containing living cells like TransCyte® (fibroblasts), Apligraft® (fibroblasts, keratinocytes), and Epicel™ (epidermal keratinocytes).

The strategies in research today for repairing skin defects can be generally classified into acellular implants and cell-loaded implants. Nowadays, researchers are looking into technologies to encourage vascularization in skin substitutes for better clinic outcomes. In the research of Wang et al., gentamicin and rhVEGF are designed to be included in PLGA microsphere-based scaffolds, which efficiently promote fibroblast adhesion and proliferation while also acting as an antibacterial agent against Staphylococci and Serratia marcescens [112]. Zhang et al. have prepared polydopamine/puerarin (PDA/PUE) nanoparticle-incorporated polyethylene glycol diacrylate hybrid hydrogel (PEG-DA/PDA/PUE) and used them as wound healing materials. This hydrogel was demonstrated to accelerate the regeneration process of skin defects in vivo in a rat model of skin defects [111] (Fig. 7h). Ali Golchin et al. combined electrospun curcumin (Cur) with chitosan/polyvinyl alcohol/carbofuran/polycaprolactone nanofibers and inoculated the scaffold with mesenchymal stem cells (BFP-MSCs). In a mouse model, such scaffolds promoted tissue proliferation as well as collagen and epithelial production, with higher wound healing efficiency [218]. Wang et al. fabricated silk fibroin (SF) scaffolds loaded with adenovirus vectors that contain VEGF165 and Ang-1 genes. In a rat skin model, it could be observed that the scaffold effectively stimulates the formation of vascular networks, thereby accelerating the regeneration of the skin [219]. Li et al. created endothelial cell (EC)-seeded SF scaffolds with a nanofibrous microstructure, and implanted the scaffolds for the repair of rat skin defects. They proved that the multiscale hierarchical design as well as cell seeding could promote neovascularization and skin reconstruction [220].

#### *2.3.3 Vascular and nervous tissue regeneration*

*2.3.3.1 Nervous tissue regeneration* Nerves are the tissues that regulate the physiological activities of the body accordingly thus dominating the sensory and motor functions of organs. Therefore, function restoration is an essential topic in nervous tissue regeneration, In the oral and maxillofacial region, the most crucial nerves are considered to be the facial nerve and the pulp nerves.

Regeneration of facial nerve can be broadly divided into two major strategies: autologous nerve grafting and nerve conduit grafting. Multiple surgeries, nerve torsion, and damaged tissue in the donor location continue to be problems of autologous nerve grafting, making it difficult to satisfactorily restore local function. Previous nerve conduits were focused on improving the repair through biocompatibility and morphological similarity to the material. In recent years, the combination of conduits with neurotrophic factors, conductive materials, or cells has been gradually investigated to achieve nerve function restoration to a greater extent. Zhang et al. analyzed the efficiency of collagen/β-TCP conduits in bridging the gap of facial nerves. They suggested that the conduits provided a promising tubular microenvironment for nerve regeneration [221]. Ma et al. developed a rat tail-derived collagen conduit, immobilizing glial cell-derived neurotrophic factor (GDNF) in the conduit to enable controlled release of GDNF. According to the results, the conduit significantly improved nerve regeneration and can degrade generally without severe inflammation [222]. Mu et al. have created a three-dimensional hierarchically arranged fibrin nanofibrous hydrogel (AFG) that resembled a neural extracellular matrix (ECM). In a rabbit facial nerve lesion model, scientists employed AFG to imitate the structure of natural fibrin cables in chitosan tubules (CST). The findings showed that AFG and CST were compatible with supporting the adhesion and growth of Schwann cells (SCs) [223] (Fig. 7i). Hiroshi Fujimaki et al. made an artificial nerve conduit by filling dedifferentiated adipose (DFAT) cells into the polyglycolic acid (PGA) conduit. By applying this conduit to a rat facial nerve defect model, the researchers demonstrated that this kind of conduit can promote axonal growth and maturation, as well as enhance physiological functions [224].

Traditional pulp regeneration was performed mainly by induction of stem cell migration through implantation of cell-free scaffolds loading induction factors. Subsequently, pulp regeneration based on cell-laden scaffolds became mainstream. Nowadays, scientists are researching methods to combine techniques such as cell 3D culture with novel materials for pulp regeneration. Nisarat Ruangsawasdi et al. have used fibrin gel scaffolds with stem cell factor (SCF) to facilitate cell homing and regeneration of a functional pulp [225]. Wang et al. fabricated a hydroxypropyl chitin (HPCH)/chitin whisker (CW) thermosensitive hydrogel with exosomes loaded. The experiments illustrated that the exosome-laden hydrogel showed an ability to promote the formation of new dental pulp-like tissues [226]. Zhu et al. implanted hydrogels carrying swine dental pulp stem cells (sDPSCs) into a mini swine root canal for pulp regeneration. According to their findings, the generation of pulp-like tissue with a layer of newly deposited dentin-like (rD) tissue along

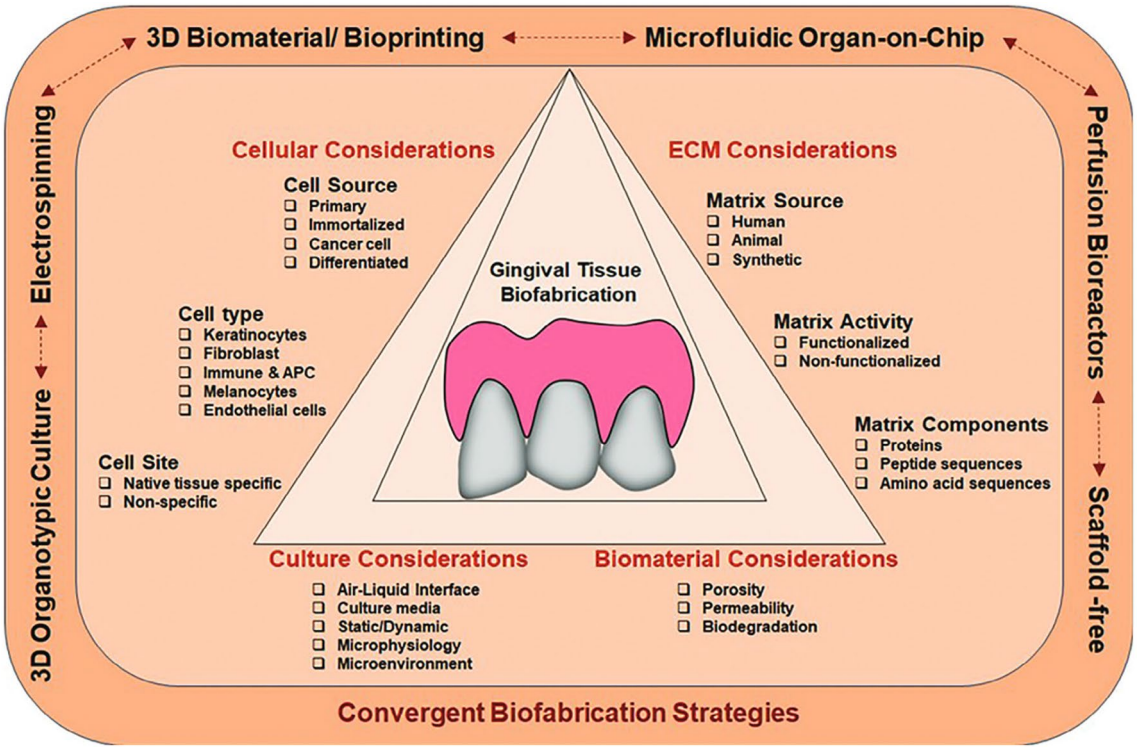



**Fig. 8** Schematic highlighting the key consideration and growing trend for manufacturing technologies[232]

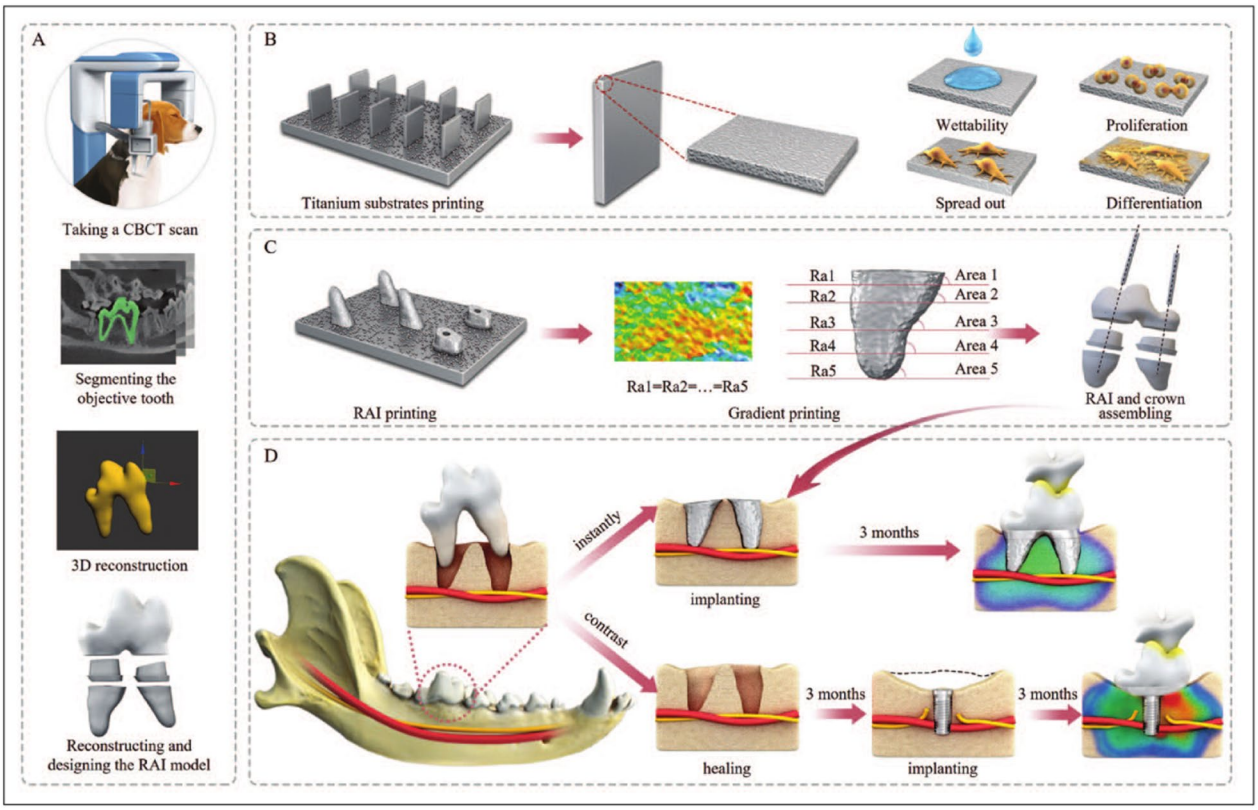



**Fig. 9** Schematic of the research procedure of two-stage root analog implants [233]

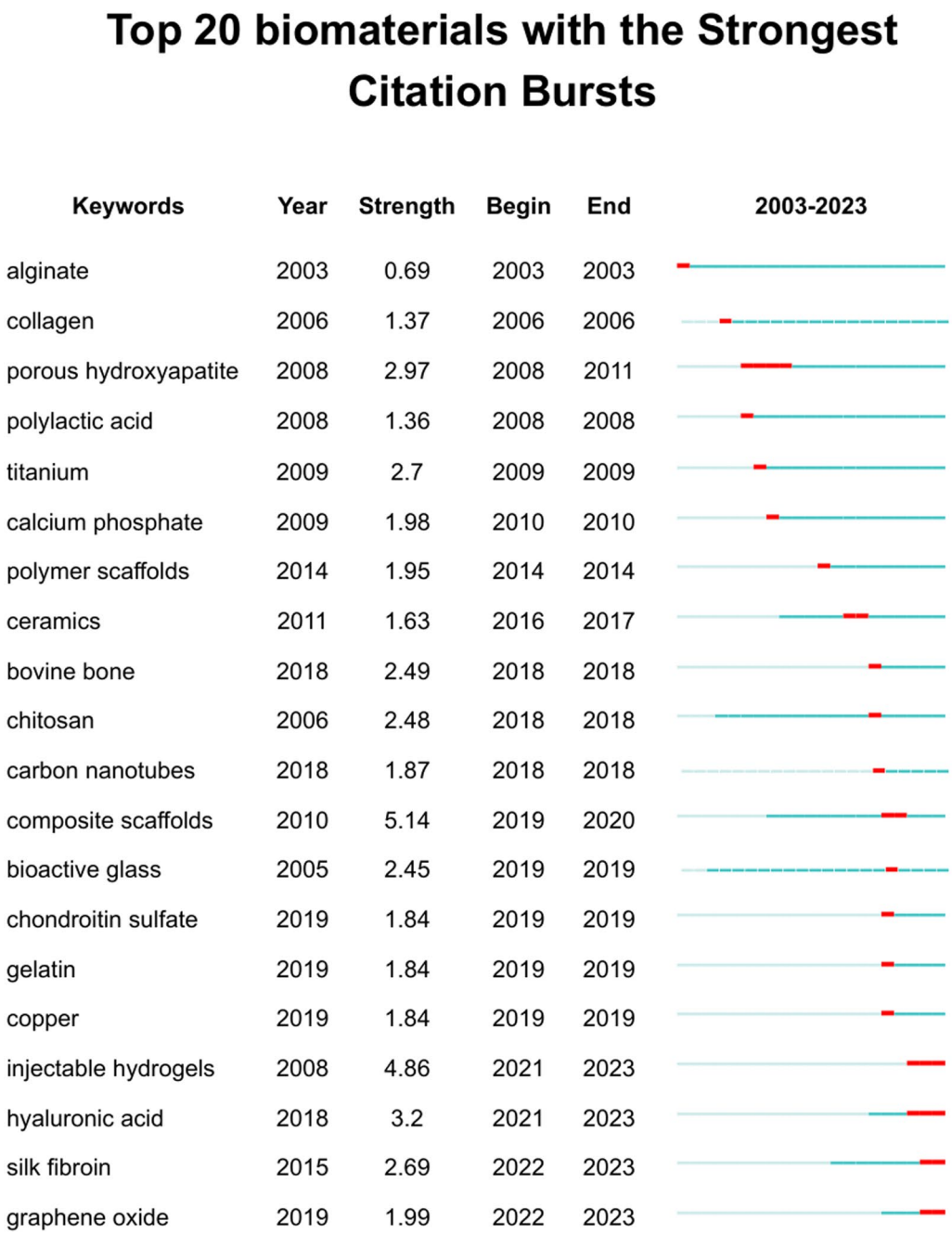



**Fig. 10** Top 20 biomaterials with the strongest citation bursts

the canal walls could be observed [227]. Yang et al. successfully prepared 3D GelMA microspheres encapsulating hDPSCs by the electrostatic microdroplet method. The microspheres could encourage new pulp-dental tissue generation in vivo, providing a possibility for future pulp regeneration applications [103]. Gong et al. successfully employed DLP to produce hDPSC-loaded GelMA microspheres and proved that the microspheres were promising in full-length dental pulp regeneration [228].

*2.3.3.2 vascularization* The lack of vascularization is a significant barrier to tissue engineering that still exists. Cell viability can be preserved in tiny implants by diffusion of nutrients and oxygen from the pre-existing vascular system. But the cells die when this diffusion only

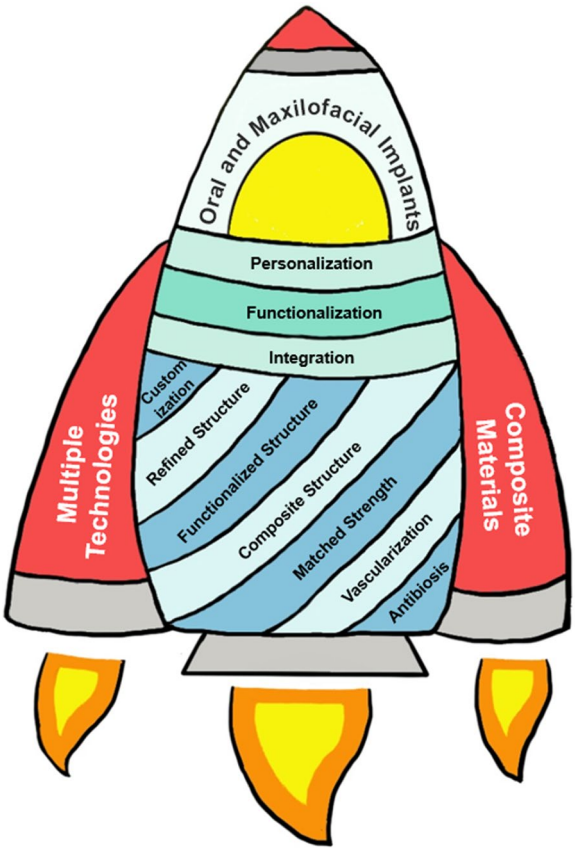



**Fig. 11** Advancements and challenges in biomaterials and manufacturing technologies for oral tissue engineering

reaches the outside layer of cells in larger implants [229]. Insufficient vascularization may lead to implant infection, partial necrosis, or even complete loosening.

There are several major strategies for graft vascularization. The hot topic of research has evolved from structure simulation, the application of bioactive molecules, to the total reconstruction of vessels. Zheng et al. produced a hydrogel-based microvascular structure with layered and branching channels with the help of inkjet printing. The minimum characteristic size of the structure is 30 μm, which is roughly equivalent to the scale of natural capillaries [230]. Shao et al. prepared morphologically controlled GelMA microfibers encapsulated in calcium alginate using a coaxial bioprinting method. These microfibers were used to create microscopic tissues containing human umbilical vein endothelial cells, forming a vascular-like lumen [104]. Mitchell A. Kuss et al. encapsulated human adipose-derived mesenchymal stem cells (ADMSC) and human umbilical vein endothelial cells (HUVEC) in a 3D printed PCL/HAp and bioactive hydrogel composite scaffold. According to the result, this material promoted the formation and anastomosis of microvessels and blood vessels [231]. Ye et al. proposed a hierarchical vascularized engineered bone (HVEB) consisting of angiogenic and osteogenic modules to achieve innovative and efficient vascularization. The sonic hedgehog (Shh) signaling pathway in HVEB was activated, and endothelial cells (EC) successfully infiltrated the osteogenic module and created a capillary network in the angiogenic module [172]. Sun et al. have successfully developed artificial branching vessel structures using digital light processing bioprinting (DLPBP). The branching vessel possessed excellent precision, mechanical properties, as well as biocompatibility, and HUVECs could attach and proliferate perfectly on the structure [51] (Fig. 7j).

## 3 Future directions

Biomaterials are a promising application of tissue engineering to address clinical problems. Although generally, significant progress has been made in recent years in biomaterials of this field, many challenges remain for future research. Foremost among these is how to keep these strategies progressing, gradually replacing the gold standard of autologous grafts and completing their successful translation from bench to bedside in oral and maxillofacial applications.

The existing problems can be mainly described into three major parts. (I) Biomaterials are evolving from homogeneous materials to multiple composite materials, from inorganic to organic, and finally to bioactive materials. But the variety of existing biomaterials and the complexity of their composites also have posed a greater challenge to researchers and manufacturers. (II) Manufacturing technology has also gone from a single technology to the concept of biofabrication, in which multiple technologies integrated (Fig. 8). The structure of the produced biomaterials is becoming increasingly refined and functionalized. However, the complex and time-consuming technical processes as well as high costs are still annoying obstacles. (III) Personalized products often depend on the technology of a particular laboratory so they cannot be mass-produced for extensive clinical and experimental applications. In addition, the contradiction between mass production and material stability also leads to the fact that the safety, biological properties, and accuracy of the material are not well guaranteed in practical applications.

So far, biomaterials have a promising future, and future research might begin with the following considerations: (I) Applying surface modification and other techniques to overcome the shortcomings of existing materials, while designing and developing more biomaterials with excellent properties. (II) Promoting research on biomaterials that are individually constructed according to the

specific conditions of patients. For example, the authors' research group has fabricated a personalized two-stage root analog implant, which is currently in the clinical trial stage (Fig. 9). (III) Determine the most effective regeneration techniques for various tissues based on their types, structures, and functions. Meanwhile, mechanism studies should also be conducted to provide precise control of cellular mechanisms. (IV) Interdisciplinary approaches are essential for the in-depth study of biomaterials, which can exploit the superiority of different disciplines, with material science and biomanufacturing technologies serving as the best examples.

In summary, since manufacturing biomaterials with excellent physicochemical properties and biological functions to meet clinical needs is our ultimate goal, achieving personalization, functionalization and integration of biomaterials are future directions in this field. The realization of these three aspects requires us to start with both multiple technologies and composite materials to achieve high mechanical strength, antibiosis and vascularization of materials, as well as refined, functionalized, composite, and customized structure of products (Figs. 10, 11).

## 4 Conclusions

Significant progress has been made in the field of biomaterials after decades of continuous research in oral tissue engineering. Biomaterials with personalization, functionalization, and integration are considered as the future direction to meet clinical needs and solve clinical problems. Among them, hydrogels and composite materials are relatively promising. Emerging manufacturing technologies-such as digitalization, microfluidics, and 3D printing-have also gained high recognition in recent years. These technologies have proven to be valuable in the development of high-performance biomaterials that support regenerative and personalized medicine. However, a number of obstacles still stand in the way of further research into biomaterials and manufacturing technologies, including time-consuming technical processes and high costs, which limit their large-scale clinical applications. It will help to replace the needs for autografts in future clinical treatments by achieving high mechanical strength, antimicrobialization, and vascularization of materials, as well as refined, functional, composite, and customized structures of products.

**Abbreviations**

| | |
|---|---|
| 3D | Three-dimensional |
| FFB | Fresh frozen bone |
| FDBA | Freeze-dried bone |
| DFDBA | Decalcified freeze-dried bone |
| GBR | Guided bone regeneration |
| PTFE | Polytetrafluoroethylene |
| nMgO | Magnesium oxide nanoparticles |
| PLA | Polylactic acid |
| PTH | Parathyroid hormone |
| PCL | Polycaprolactone |
| SS | Stainless steel |
| Co–Cr | Cobalt–chromium |
| HA | Hydroxyapatite |
| TCP | Tricalcium phosphate |
| BCP | Biphasic calcium phosphate ceramics |
| DCPD | Dicalcium phosphate dihydrate |
| BG | Bioactive glass |
| BFP | Bone-forming peptide |
| PGA | Polyglycolic acid |
| PEG | Polyethylene glycol |
| PTFE | Polytetrafluoroethylene |
| PE | Polyethylene |
| PMMA | Polymethyl methacrylate |
| PEEK | Polyetheretherketone |
| PLGA | Poly(lactic acid) poly(glycolic acid) |
| Ang | Angiopep |
| Tyr | Tyrosine |
| DLP | Digital light processing |
| GelMA | Methacrylate-based gelatin |
| MET | Metronidazole benzoate |
| PRF | Platelet-rich fibrin |
| BMP | Bone morphogenetic protein |
| VEGF | Vascular endothelial growth factor |
| bFGF | Basic fibroblast growth factor |
| IGF | Insulin-like growth factor |
| PDGF | Platelet-derived growth factor |
| EMDs | Enamel matrix derivatives |
| SilMA | Silk fibroin glycidyl methacrylate |
| TG | Trigeminal gangliak |
| Alg | Alginate |
| Lap | Laponite |
| CNF | Carbon nanofibers |
| SLS | Selective laser sintering |
| SLM | Selective laser melting |
| Met | Metronidazole |
| BSP | Phosphate sodium |
| BDP | Betamethasone 17,21-dipropionate |
| ICG | Indocyanine green |
| ROP | Ring-opening polymerization |
| FLASH | Fluorescently labeled sensitive hydrogel |
| PDA | Polydopamine |
| PUE | Puerarin |
| FITC | Fluorescein isothiocyanate isomer |
| PEO | Plasma-assisted anodizing |
| BMSCs | Bone marrow-derived stem cells |
| ECM | Extracellular matrix |
| PIE | Peri-implant epithelium |
| TMD | Temporomandibular disorders |
| FDM | Fused deposition modeling |
| ITOP | Integrated tissue organ printer |
| MSs | Hydrogel microspheres |
| 4D | Four-dimensional |
| EPCs | Endothelial progenitor cells |
| GO | Graphene oxide |
| TMJ | Temporomandibular joint |
| ADSCs | Adipose tissue-derived stem cells |
| SF | Silk fibroin |
| EC | Endothelial cell |
| SCF | Stem cell factor |
| sDPSCs | Swine dental pulp stem cells |

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**Author contributions**

MS and LKT were involved in data curation, formal analysis, literature exploring and writing; XFY, JYL, and HHH were involved in literature exploring and project administration; MFY, YH, and JL contributed to conceptualization and supervision.

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**Availability of data and material**
The original data involved in the manuscript can be obtained from references.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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