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Recent advances in natural polymer-based hydroxyapatite scaffolds: Properties and applications

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ABSTRACT

New materials that mimic natural bone properties, matching functional, mechanical, and biological properties have been continuously developed to rehabilitate bone defects. Desirably, 'tissue engineering' has been a multidisciplinary ground that uses the principles of life sciences and engineering for the biological replacements that restore or replace the tissue function or a whole organ. Nevertheless, the bone grafting treatment has numerous restrictions, counting the major hazards of morbidity from the sites where donor bone grafts are removed, the likelihood for an immune rejection or bacterial transport from the donor site (in case of allogeneic grafting), and the inadequate availability of donor bone grafts that can meet the current demands. Since the proper growth of synthetic materials for implantable bones encourages the reconstruction of bone tissues by providing strong structural support without any damages to the interferences of biological tissue. To serve for such behavior, the biodegradable matrices provide temporary scaffolds within which the bone tissues can be regenerated. Typically, the thermoplastic aliphatic polyesters are found to serve this purpose. The great significance of this field lies in the *in vitro* growth of precise cells on porous matrices (scaffolds) to generate three-dimensional (3D) tissues that can be entrenched into the location of tissue/bone damage. Numerous gifts have been gifted by our nature to advance and preserve the well-being of all living things either directly or indirectly. This review focuses on the recent advances in polymer-based hydroxyapatite scaffolds including their properties and applications.

1. Introduction

Tissue and bone defects in the human body can result from pathogenic or trauma and it requires treatment for possible repair, replacement, or regeneration. Conventional treatment normally targets transplantation of tissue from one position to another position in the same patient (autograft) or from one individual to another (allograft). Despite being revolutionary and lifesaving, both the techniques (autograft or allograft), have some inherent issues. The autograft harvesting procedures are costly, constrained by anatomical restrictions, and introduce donor side injuries. Likewise, the allograft is limited by access to sufficient and suitable tissue for the patients' defects. Furthermore, there are risks associated with disease transmission from donor and allograft rejection by the patient. On the other hand, the specialized area

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of tissue engineering focuses on the replacement and regeneration of injured tissues by developing materials and bone grafts that can restore, preserve, and enhance tissue functions. This technology avoids various problems associated with autograft and allograft replacement during bone gap repair [1,2]. The "National Science Foundation workshop" in 1988 formally coined the terminology 'tissue engineering' to denote the application of ideology and techniques in engineering as well as life sciences for the primary understanding of structural and functional interaction in typical and pathological mammalian tissues and the improvement of biological substitutes to re-establish, sustain or to improve the tissue function applications [3]. Nevertheless, the specialization of tissue engineering is never a new process, the ideology of substituting tissues with another goes back as far as the 16th century, where they replaced a nose assembled from a forearm flap in the year 1597 and thereby published their work 'De Custor Chirurigia per Insitionem' in the same year [4]. It is a multidisciplinary field, gathering experts mutually from engineering and life sciences. The field of tissue engineering depends on a great deal of the understanding and use of 3D porous scaffolding materials to endow with appropriate surroundings for tissue and organ rejuvenation [5]. The cells, signals, and scaffold unification are frequently adopted in tissue engineering (Fig. 1).

2. Bone structure, function, and pathology

Bone consists of a marrow-filled centre surrounded by spongy mineralized tissue called trabecular bone and another outer layer of compact mineralized tissue called cortical bone. Aschematic representation of the internal structure of bone is shown in Fig. 2. The bone marrow is mainly consisting of hematopoietic cells and mesenchymal

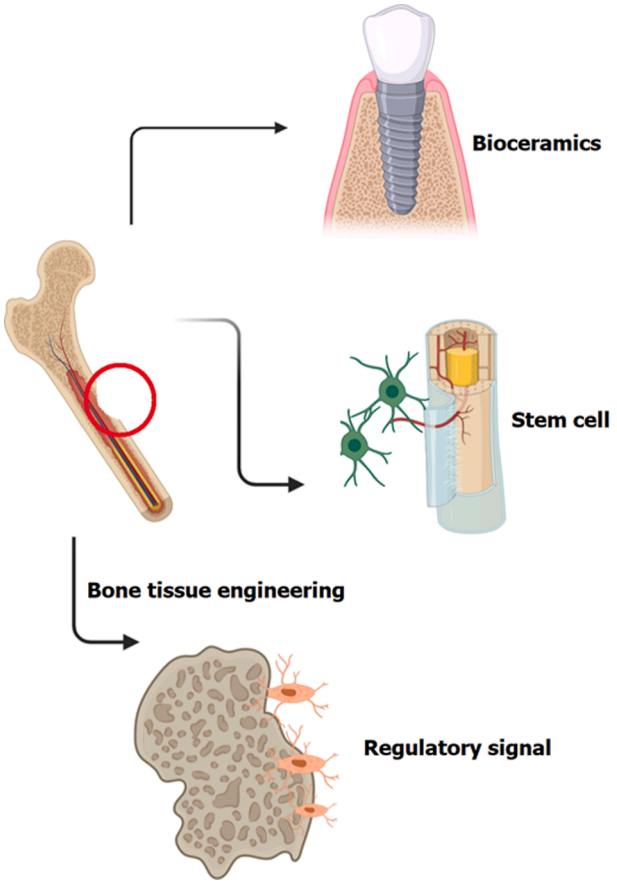

Fig. 1. Schematic representation of tissue engineering approach that can be used for the development of teeth implants, bone tissues, and restoration of regulatory signals.

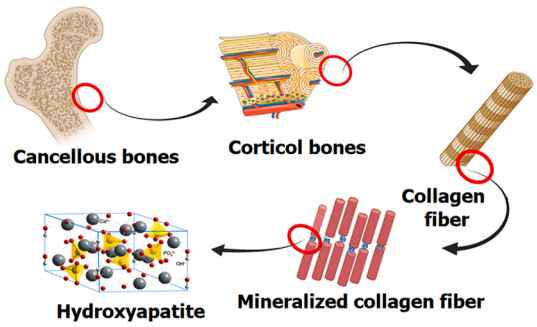

Fig. 2. Schematic representation of the internal structure of bone containing cortical bones, collagen fiber, and mineralized collagen fiber.

stromal cells and supplied by a vascular network that ensures enough blood circulation throughout the skeletal system [5,6]. It is found that the woven (trabecular) bone calcifies and matures into lamellar (cortical) bone [7]. Acids and enzymes compartmentalize and deteriorate the organic and inorganic matters of the bone, in which the osteoclasts derived from monocytes supervise bone resorption. New bone matrix deposition is orchestrated at these resorption sites by osteoblasts of mesenchymal origin [8].

Once the bone deposition is complete, a portion of the osteoblast goes through the apoptosis process, while the remaining portion of osteoblasts combine into the bone matrix and turn into either osteocyte or lining cells that are involved in mechanical load sensing [9]. The bone functions are mainly facilitating movement, protect vital organs, the reservoir of bone marrow, storage of minerals, and provide the support structure for the body. The bone remodelling process enables bone to have self-repair capacity in the case of fractures or defects [10]. Unfortunately, the intrinsic healing ability is limited and inadequate for the repair of extensive injury due to trauma, disease, and tumor such as in the case of non-union fractures, which may occur due to longer than usual fracture, bone fragment loss, inadequate vascularity, and soft tissue coverage, or infection. Besides, the displaced bones need realignment and maybe additional load-bearing support, which otherwise will cause the bone to be unstable, not able to heal itself, and succumb to excessive mechanical forces [11]. Besides injury, bone-related diseases, which result from a disruption in the normal bone remodelling process, may also necessitate further clinical intervention.

3. Biomaterials

The biomaterial was initially defined as 'a nonviable material used in a medical device, proposed to interrelate with biological systems' by the European Society for Biomaterials (ESB) in 1976. However, the ESB's current definition is 'a material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body. This delicate change of definition signifies the evolution of the biomaterial field that of moving from merely acting as material that interacts with the body to material that influences biological process with aim of functional restoration of tissue and organs. The three groups of biomaterials used in the tissue engineering field are natural polymers, synthetic polymers, and ceramics. As each of the biomaterial groups has its advantage and disadvantage, the use of composite materials in the fabrication of scaffolds provides an advantage of controlling the material property. Ceramic materials e.g. hydroxyapatite (HAP) and tri-calcium phosphate (TCP) and their composites hold high potentials for biomedical applications such as artificial bone grafts, bone implants, bone tissue engineering scaffolds, and so on. Ceramic scaffolds generally exhibit high mechanical strength, low elasticity, and brittleness. As ceramic materials display similar chemical and structural characteristics to that of native bone, these materials are highly biocompatible and functionally suitable for bone

tissue engineering. Furthermore, ceramics are also proven to enhance the growth and differentiation of osteoblasts [5,12]. HAP is a primary constituent of bone and may seem to be ideal as a substitute for a bone graft. In dental and orthopaedic surgery, various ceramics have been used to fill bone defects and to cover metallic implant surfaces to improve the integration of implants with the host bone. However, their clinical tissue engineering applications have been limited due to their fragility, implantation shaping difficulty and the new bone formed in a porous HAP network cannot sustain the mechanical load needed for remodeling[13,14].

4. HAP and its general properties

Of all the calcium phosphate cement types, HAP bioceramic has chemical constituents of bones and hard tissues in mammals. HAP is one of the few bio-materials that are regarded as biodegradable bioceramic, which promotes development and osteointegration when used as implants in the orthopedic, dental, or maxillofacial field [15]. The surface of the HAP implant exposed to the surrounding environment binds to natural apatite in the body and thereby promotes bone formation in the case of orthopaedic implants. By altering various parameters in the process of syntheses such as sintering temperatures, pH, concentrations of the solution, and time, the mechanical characteristics of HAP bioceramics can be altered/controlled. The HAP implants are on the whole sintered to improve their mechanical characteristics. Sintering temperature below 800 °C results in the scaffold with lowered mechanical strength but enhanced *in vivo* biodegradability, which could be due to the presence of other forms of calcium phosphate in the ceramic graft; HAP possesses the least bio-degradability [16]. Since HAP is stable under an *in vivo* environment, it is commonly endorsed as a coating material for metallic implants (generally titanium and stainless alloys) to modify the surface morphological characteristics and formulate the implant to further enhance the biological activity [17].

HAP is one of the most stable calcium phosphate minerals at room temperature and pH above 4.2 [18,19]. HAP [$Ca_{10}(PO_4)_6(OH)_2$] has a Ca/P molar ratio of 1.67 and mostly have a hexagonal crystal structure. The other crystal structure of HAP is monoclinic form. The most important difference between these structures is the orientations of the hydroxyl groups (OHs). In monoclinic HAP, all hydroxyl groups have the same direction in the same column and the opposite direction among columns while, in hexagonal crystal structure neighbouring hydroxyl groups point in the opposite direction [20]. The schematic representation of the crystal structure of HAP crystal is shown in Fig. 3. The different crystalline structure of HAP enables it to present wide compositional variations in a biological system such as in bone, with the ability to accept many different ions in its three sub-lattices [21,22].

Bearing in mind that the main constituents of the natural bone are collagen fibers and HAP crystals, and in that way, the nano-HAP has excellent properties such as biocompatibility and bioactivity that are crucial for cell development [23]. Consequently, the inorganic/organic composite materials enclose a greater potential for bone tissue engineering application. Numerous scaffolds have been fabricated by directly mixing the composite active additives but leads to uncontrolled homogeneity in the polymer matrix [24–26].

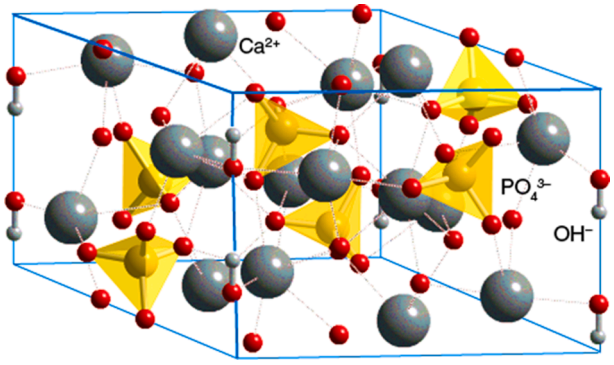

Fig. 3. Schematic representation of the crystal structure of the HAP compound.

5. Scaffold properties

5.1. Physico-mechanical properties

During implantation, the mechanical properties of the scaffold should prevail to enable the surgical procedure. The manufacturing of scaffolds with the required mechanical properties is one of the biggest challenges to engineer bone or cartilage. Once it is implanted, it should maintain the necessary mechanical integrity within the host tissues until the next surgery [27]. The second challenge is that healing rates differ from person to person depending on the age factor. For example, the bone of a youngster has a better healing capacity more than the elderly. Considering these challenges, scaffolds on reliable materials must be manufactured having mechanical properties fulfilling the desired qualities. Unfortunately, many materials may fail after implantation due to their insufficient vascular capacity. The success depends on the balance between the scaffold's porous architecture and mechanical properties that allow cell infiltration [28]. HAP is brittle polycrystalline material and the mechanical properties are influenced by grain size, crystallinity, grain boundaries, composition, and porosity [29]. HAP ceramics are sensitive to cracks due to the brittle nature and inability for plastic deformation. HAP has high strength ionic bonds, which confer its brittleness. Thus, the slightest crack will be propagated and will fail the scaffold [29]. Same as other bioceramics, the strength, and toughness of the sintered HAP scaffold increase with the decreasing HAP grain size [30]. As finer grains produce material with smaller grain boundary flaws, scaffold with finer grain size has higher strength compared to scaffolds made of larger grains size. Similarly, a scaffold with high crystallinity content and a low porosity will have higher stiffness, tensile strength, compressive strength, and fracture toughness compared to the scaffold with a higher amorphous phase and higher porosity content. The mechanical properties have been elaborated extensively by Dorozhkin [23].

5.2. Biological properties of HAPs

HAP holds high potential and has been extensively used as bone grafting and substitute materials, due to its inherent biological properties including biocompatibility, bioaffinity, bioactivity, osteoconductivity, osteointegration, and certain conditions of osteoinduction. There is no implantation toxicity as HAP contains calcium, phosphate, and hydroxyl ions, which are the elements that naturally present in the human body. When HAP is implanted in the human body through a carbonated calcium-deficient layer of apatite at the bone/implant interface, the newly formed bone binds directly to the implant. The bonding of bone directly to an implant material is activated by the formation of the apatite layer. Amorphous or hydroxyl carbonated calcium phosphate is formed in the apatite layer when the implant surface is immersed in simulated body fluid (SBF), which leads to HAP *in vitro* bioactivity. The mechanism is associated with the formation of the apatite layer, due to the partial dissolution of HAP and ion exchanges between SBF solution and HAP surface. Antibiotic, anti-cancer, and gene therapy delivery vehicles are among the applications of HAP scaffolds due to their ability to dissolve slowly at the target site [13,31].

6. Porous HAPs

Bone substitutes should have a network of interconnected pores to enable infiltration of host cells, diffusion of nutrients and oxygen, and removal of waste material. The pore structure of the bone scaffold plays an important part in osteoblasts infiltration, adhesion, proliferation, and

differentiation in the scaffold, which leads to successful osteointegration and bone regeneration [16,27]. The pore structure of a scaffold refers to its pore size, porosity, pore, pore interconnectedness, pore distribution, and surface area scaffold. Scaffolds with suitable porosity and surface area act as the temporary template for the seed or host cell attachment and proliferation, nutrient and oxygen diffusion, excreted waste removal, and followed by extracellular matrix deposition, ingrowth of vascular tissue, and neural network [32]. Although high porosity increases the cell infiltration, the mechanical strength of the scaffold reduces exponentially with increasing porosity. Thus, a scaffold with porosity $>$ 80% is not suitable as a bone substitute. The normal human bone unit average size is about 223 μm, and various studies suggest that scaffolds with pore sizes between 200 and 800 μm are suitable to function as a bone substitute [33]. The pores are categorized based on the size like micropores, mesoporous and macroporous, which are less than 2 nm, 2–50 nm, and greater than 50 nm, in accordance with the International Union of Physical and Applied Chemistry (IUPAC) classification. Since the invention of nanotechnology, the minute pores are called nanopores (range is between 1 and 100 nm), and the materials having such pores are known as nanoporous materials. Studies have been done on practicing molecular templates on the size and morphology of the particle [34–36]. An initial study on porous HAP started with macroporous HAP (pore width $>$ 50 nm) that can be useful for the drug delivery system because (a) it is biocompatible, (b) ability to control the pore sizes within the scaffold to regulate the release rate, and (c) it does not interact or modify the drug [37]. Another important criterion is the specific surface area. HAP scaffolds fabricated by sintering normally need the incorporation of ligands that enhance subsequent cell adherence to the scaffold. The available surface area within a pore influences the ligand density in the pore and the amount of cells that can adhere to the ligand. Thus, the scaffold pore size should be optimum e.g. large enough to allow cells to migrate into the pore structure while small enough to maximize the specific surface area [3].

7. Scaffold requirements

In the medical field, scaffolds are manufactured from various biomaterials employing a variety of techniques for a wide range of applications to regenerate numerous tissues and organs in the body. The scaffolding material properties are enlisted below: (i) Biocompatibility is the process of evading the residual exhibition of tissue disclosure to the prosthesis [38], (ii) it must possess exemplary surface chemistry to permit addition, recession, propagation and variation of cells [39], (iii) analogous pores of appropriate shape to promote vascularization and cell incursion [40,41], (iv) organized biodegradability to enhance the composition of a different tissue [42], (v) sufficient mechanical qualities to cultivate the system actively, follow instantly and thoroughly refurbish the implantation [24,42], (vi) promote the requisite mechanical factors to contribute to the improvement of the surrounding cells, distribute the preparatory molecules to the overhaul place and contribute suggestions to restrict the system and activity of the developed tissue [43], (vii) enhance the development of ECM by stimulating cellular behaviour and possess the capability to contribute the molecular signals to the cells [5].

8. Scaffold synthesis methods

Conventionally, compact and dense HAP scaffolds are prepared by compressing the HAP powders under high temperature, pressure, and varied holding period at the sintering temperature. Also, the sintering conditions, such as the temperature, pressure, and holding period, the starting material properties such as the HAP grain size, shape, preparation method, and additive used, decide the final characteristics of the final ceramic scaffold [44]. Due to the growing importance and application of HAP bioceramic scaffolds, diverse synthesis processes have been explored to prepare HAP scaffold, which includes polymeric replication method [18,22,44–48], freeze-drying [49,50], solvent casting and particle leaching [37], electrospinning [51–54], thermal-induced phase separation [55,56] and rapid prototyping [57–59]. However, the fabricated porous bodies should meet the essential properties such as the required shape and size of pores appropriate for targeted applications. Besides that, the supercritical CO_2 foaming and melt processing is also able to fabricate porous scaffolds with varied pore sizes by changing the molecular weight of polymer with compatible mechanical strength. Normally various synthetic polymers are combined with HAP to produce bone substitutes using this method.

In general, the 3D scaffolds are the basic construct for tissue engineering and by taking advantage of this property, the synthesis methods for the formation of scaffolds may vary. There have been several synthesis techniques which are in practice for scaffold fabrication including electrospinning, phase separation (solid and solid–liquid separation), self-assembly, lithography, rapid prototyping (fused deposition modeling, 3D printing, selective laser sintering, and stereolithography), solvent casting, and freeze-drying/lyophilization [60]. For a majority of these methods, each has its advantages and disadvantages, and therefore, considering the merits and demerits of existing scaffold fabrication techniques, the freeze-drying, and solvent casting techniques are mostly used.

8.1. Freeze-drying

Freeze-drying/lyophilization is the drying process under extremely low temperatures and this technique could be used to fabricate porous scaffolds from the solutions. The freeze-drying process is under practice in the past two decades for the fabrication of tissue engineering constructs and is the phase separation process based on temperature. Also, the phase separation in this technique can be liquid–liquid or a solid–liquid process where the solvent freezes leaving behind the concentrated solid polymer phase. The frozen solvent phase sublimates under vacuum, resulting in a porous structure and the porosity and pore size of the lyophilized scaffolds depends on pH and rate of pre-freezing and lyophilization. The rapid freezing will lead to scaffolds with small pores and that too the structure and morphology of scaffolds vary depending upon the solvent type, polymer concentration, and freezing profile [61].

8.2. Solvent casting

Solvent casting is the simplest and inexpensive technique to produce scaffolds in the form of films and this can be used in the case of polymers dissolved in organic solvents. The polymer solution will be cast in the mold and left undisturbed for the complete evaporation of the solvent. The solvent casting technique does not produce any pores and by making use of this technique, the scaffold may retain the solvent toxicity and the inclusion of the leaching step may be time-consuming [62].

8.3. Surface modification

The various biodegradable composite scaffolds were in use as biomaterials for tissue engineering and drug delivery applications. These scaffolds generally possess good bulk properties but lack in providing vital surface properties needed for tissue engineering applications. The biomaterial surface generally lacks cell recognition sites and so, the scaffold's surface modification is very essential to control the cell-material interaction. Since the cells can sense the microenvironment where they exist and respond to the surface morphology and chemical cues. Based on this, surface properties such as nano or microtopography, surface chemistry, and cell adhesive sites are vital for efficient tissue regeneration [63]. The modification of surface chemistry tends to alter the surface wettability of the scaffolds and thus by tuning the wettability behaviour, good protein adsorption can be attained which in turn favours the initial cell attachment. Also, the surface of polymers can be modified by physical, chemical, mechanical, or biological modification

methods as provided in Table 1, where each modification method has its advantages and disadvantages [64].

In recent years, the modification of polymer surface by irradiating the surface with accelerated ions has been increasing and still been under exploration for selected polymers with advanced biomedical applications. The methods mentioned in Table 1 could greatly modify the surface chemistry, morphology, topography, and properties such a luminescence and conductivity [64]. Also, in the case of surface modification with accelerated ions, the high energy ions will be created in a vacuum from an ion source, which will further be accelerated to produce ion beams and these ions react with the atomic structure of the polymer surface, leaving behind the modifications on the polymer surface. In the case of low energy ion treatment, the ions pass through few nanometres while passing the high energy, the ions create modification up to few micrometers in the polymer surface [64]. The depth of ions penetration depends upon the mass and energy of passing ions [65] and also, the cells attached to the micro and nano topographic structures and can grow further and infiltrate through the porous structure which results in enhanced regeneration. The Kr^{+} ion irradiation of electrospun PLLA (poly-L-lactic acid) scaffolds has experienced a change in fiber diameter and damaged the bonds and so, the attachment of L929 cells got increased with an increase of irradiation fluence [66]. Further, the surface engineering of scaffolds improves cell attachment, migration, cell imaging, and cell functioning [67]. For example, the surface of the Si^{2+} ion engineered polypyrrole nanotubes has the enhanced antioxidant activities which are favourable for cancer treatment [68]. In addition, the plasma immersion ion implantation and deposition technique can easily modify the chemical, mechanical, bioactivity, hemocompatibility of many biomaterials [69].

9. Scaffolds selection for fabrication

The major criteria for any scaffold are that it should mimic the natural properties of the extracellular matrix (ECM). Almost all the cells in the human body except blood cells anchor to the ECM and develop into tissues and this ECM offers structural support and microenvironment for the anchored cells to attach, migrate, proliferate, and provide signals for cell–cell interaction. It also provides mechanical rigidity and elastic modulus to the growing tissues and also, the ECM regulates the biological activities by providing the biological cues to the attached cells. Besides these activities, ECM provides growth factors and ligands for the developing cells. Based on these considerations, the scaffold should be designed in such a way that should exhibit the natural properties of ECM's architectural, biological, and mechanical properties.

The architecture of the engineered scaffold should be processed to provide structural support for the regenerating tissues and the structure should possess good porosity with interconnected pores. The degradation rate of the scaffold should match the regeneration of the developing organ and for instance, the minimum regeneration period of skin is a week and so the scaffold should be stable for at least 7 days. Similarly, the bone takes a minimum of 28 days for its regeneration and in that way, the degradation rate of scaffolds for bone regeneration should be tuned in such a way that the bone degrades in a month.

The 3D scaffolds should be highly compatible, i.e., on implantation, the scaffold comes in contact with the blood and cells and therefore the engineered scaffolds should not induce any toxicity to the cells. Also, the synthesized scaffolds should support the encapsulation of biomolecules and drugs in order to provide growth factors to the growing cells and to maintain the implant site without any infection. Also, the scaffolds should interact with the cells by providing suitable sites for cell attachment and also should enable the proliferation and migration of cells in the defect site. To facilitate all these properties, the scaffold pore volume should be optimal to undergo easy vascularization.

The composite is the blend of two or more chemically different materials which includes polymers, ceramics, and metals. The biodegradable composites applied for tissue engineering must possess the mechanical properties close to the organ of interest and with that view, the metal plates are being used as implants since the early nineteenth century [70]. But the metal plates are less compatible and undergo corrosion after implantation and also the metal ions release may trigger undesirable immune responses. For controlling these issues, the metal plates are coated with polymers or ceramics [71] where the formed scaffolds should be strong enough to support the cell's attachment and proliferation. Moreover, the biopolymers in general exhibits poor mechanical stability and are lacking bioactivity and at the same time, they offer stiffness and exhibit good tensile strength, but are highly brittle and so limiting their application in hard tissue regeneration. Also, the high tensile strength of ceramics limits their application to serve as soft tissues [3] and these problems could be overcome by combining polymers with ceramics. The addition of ceramics to the polymers as fillers will certainly improve the mechanical properties of the polymers, i.e. the ceramic phase addition with polymers can facilitate the high amount of drug loading or biomolecules like proteins, cell adhesive peptides, or growth factors. Further, the incorporation of ceramic fillers alters the structural integrity, pore-volume, porosity, mechanical strength, and degradation of the scaffolds [72]. Hence, the development of composite biomaterials is much attractive as their properties can be tuned in accordance with the needs of scaffolds based on their applications.

The recent increase in the demand for artificial implants is rapidly growing in the market so as to meet the needs of organ transplantation and also due to the progressive research achieved in the tissue engineering sector. Since the composite scaffolds based on natural polymers are much useful to this sector and with that view, the polymers are engineered to overcome the disadvantages and to get the scaffolds with the desirable properties by forming composites with other polymers, metals, or ceramics. Also, the blends made from water-soluble polymers are highly susceptible to aqueous degradation resulting in complete degradation of scaffolds before reaching the proposed destination. In order to overcome these issues, the scaffolds are stabilized by crosslinking the individual molecules among themselves. On degradation, the unreacted cross-linkers may become toxic to the growing cells, and hence the synthesis of scaffolds either by physical crosslinking techniques or crosslinker free scaffolds has received much attention [73,74].

10. Binding agents used in HAP scaffolds

Binding agents or binders are substances used to hold the main material, in this case, HAP, together to form a physically or chemically unified material. Normally binders are used in HAP scaffold preparation to hold the grains together and compacted in a mould of a certain shape so that they can pass through the fabrication stem such sintering step. The binders used in the fabrication of the medical-grade scaffold should not be resulting in any unfavourable characteristics in the final scaffold such as not causing toxicity, antigenicity, abrasiveness, and not hindering the removal of the scaffold from the mould. The binders are also expected to burn out at low temperatures leaving minimal or no ash after the sintering process and enhance the mechanical properties of the final scaffold. Binders are usually sourced from inexpensive substances

Table 1
The various types of surface modifications are employed in the formation of HAP composites.

Physical	Chemical	Mechanical	Biological
Irradiation (UV, plasma, accelerated ions, electrons, heat treatment)	Etching (gas and acid etching), Chemical vapour deposition, physical vapour deposition, grafting of functional groups	Roughening, Micromanipulation using probes	Surface adsorption of biomolecules, drugs, and cell adhesive peptides

[75].

10.1. Synthetic polymers

Synthetic polymers are easily accessible and are available in enormous forms. Polymers like polystyrene [76–79], polyvinyl butyl [80,81], polyvinylpyrrolidone [82], polysulfone [83], polycaprolactone [84,85], poly (lactic acid) [86–88], polyvinyl alcohol (PVA) [48,89–92], polytetrafluoroethylene (PTFE) [93], polyethylene terephthalate (PET) [94], methylmethacrylate (PMMA) and polyethyl- (PEMA) [95] and others binders have been used previously binders in the fabrication of HAP scaffolds.

10.2. Biopolymer binders

Various natural macromolecules, called biopolymers, have been developed as binders. Biopolymers are mainly divided into two types: Polysaccharides and Proteins. The former contains alginate, pullulan, chitosan, chondroitin sulfate, etc., and the latter contains fibrin, gelatine, keratin, and collagen. They possess qualities like non-toxic monomer units and extremely biocompatible. Biopolymers are commonly manufactured from biological waste as it is abundantly available in living organisms.

10.3. Natural gums

Natural gums can be sort based on their sources as (a) marine or seaweeds based gums, such as agar, alginates, (b) microbial-based gums such as algae, bacteria, dextran, fungi, glycan, pullulan, etc., and (c) plant-based seed gums such as locust bean gum, guar gum, starch, cellulose or tree exudates gums such as ghatti gum, gum tragacanth, gum Arabia, karaya gum or tubers based gums such as potato starch and extracts based such as pectin [96,97]. A simple block diagram representing the classification of natural gums is shown in Fig. 4. For decades, plant-based and animal-based resources are utilized by researchers in the domain of medicine and pharmacy. Now, diluents, binders, tablet dispersants, suspension shielding colloids, and gelling agents are derived from polymers based on plants and animals.

The diverse number of natural gums is biocompatible, and a copious number of researchers have repeatedly tested them for synthesis of medical procedure materials such as in abrasion healing dressings material, drug deliverance systems, and further in simulated tissue engineering scaffolding. These natural polymers have outstanding biodegradability, biocompatibility, free from toxicity, and cheap and easily available [96,97]. A diverse category of natural polymer polysaccharides has been extensively used as films, nanofibers, and scaffold materials for biomedical applications [80,83,98,99].

10.3.1. Gum tragacanth

Gum tragacanth (GT) is an amalgamated polysaccharide with an ingenious biopolymer that showcases distinguished properties such as (i) biodegradable (ii) biocompatible and iii) function as thickener, stabilizer, emulsifier, and a crosslinker. It is composed of a water-absorbent segment called tragacanth acid, which is composed of 60–70%, and water-resistant segments called tragacanthin. The structure of the GT is shown in Fig. 5. GT displays excellent potential as a drug delivery vehicle and promote the wound healing process. Researchers have created nanofibrous scaffolds in the form of thin films using GT by electrospinning technique blending GT with PVA and/or poly (ε-caprolactone) (PCL) thereby exposing its amazing collagenation and proliferation in wound healing [96–99], They demonstrated that the antibacterial properties of the curcumin-loaded GT/poly (ε-caprolactone) electrospun nanofibers with controlled and prolonged curcumin release, thereby exhibiting remarkable healing rate as a dressing material [99,100]. We have also previously studied the fabrication of HAP scaffolds using GT as a natural binder and have confirmed their suitability as a bone scaffolding material for use in non-load bearing applications [18]. Fig. 6 shows the HAP scaffold prepared by the polymeric replication method using GT.

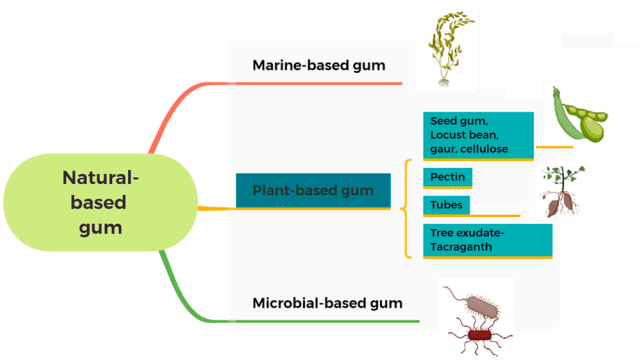

Fig. 4. Binders based on natural gums.

10.3.2. Xanthan gum (XG)

Xanthan gum (XG) belongs to an anionic polysaccharide, which can be synthesized by Gram-negative bacteria such as Xanthomonas bacteria [101]. It has a main chain identical to that of cellulose and is accompanied by side chains that comprise of 2:1 ratio of *D*-mannose and *D*-glucuronic acid [101,102]. XG-initiated materials have been appropriate to be used as an emulsifier in food, for wrapping food items, in cosmetics, as a scaffolding material in tissue regeneration application, drug delivery systems, in water-based paints, as a binder in jet injection printing, in building materials and many more [103]. Moreover, there is always a demand for biomaterials with potential enhanced properties and since XG in its pure form is biodegradable and biocompatible and utilized in a choice of biomedical applications along with other polymers for tissue regeneration applications [104]. Recently, nanocomposite fibers using xanthan gum and chitosan were fabricated by Shekar et al. for the deliverance of bioactive molecules [105]. The discharge of curcumin was analyzed for 12 h by varying the pH, it was found that no initial burst of the compound was found and the drug, curcumin demonstrated a lower discharge of drug in the pH 2.2.

10.3.3. Dextran

Dextran is a biocompatible, nontoxic, and hydrophilic polysaccharide obtained basically from bacteria. Dextran is predominantly composed of α(1 → 6)-linked d-glucopyranosyl vertebrae customized with small side chains of *D*-glucose linkages. Dextran copolymer is biocompatible as well as biodegradable that can be principally applied in biomedical and related uses to diminish the inflammatory behaviour and encourage faster wound healing treatment [106].

10.3.4. Alginate

Alginate belongs to an anionic biopolymer comprising mannuronic and glucuronic acid units in an arbitrary group [107]. The mannuronic acid and glucuronic acid units are bonded through glycosidic attachments [107,108], which make alginate biocompatible with exclusive

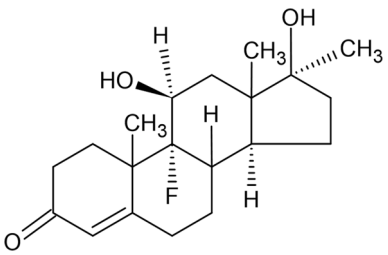

Fig. 5. Chemical structure of GT.

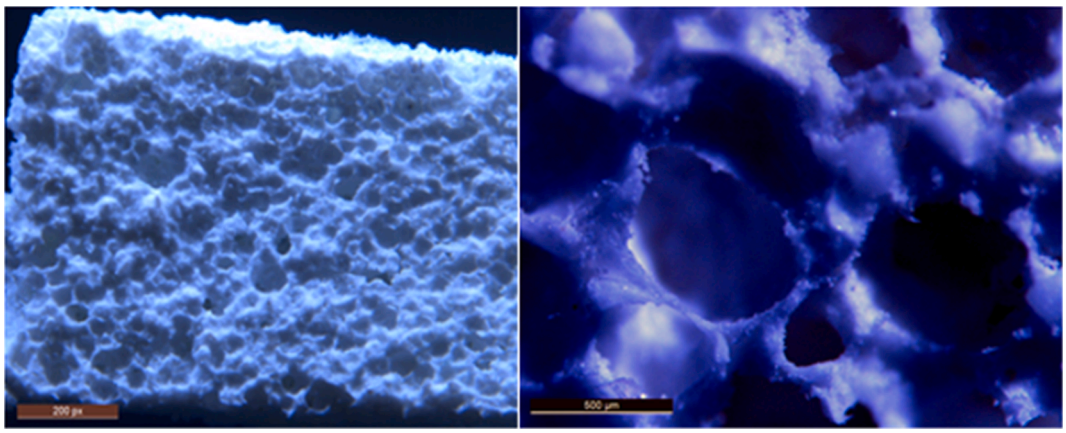

Fig. 6. Bioceramic HAP scaffolds synthesized using GT [18].

relevance's in nanomedicine and tissue engineering application. Recently Sukhodub et al., [109] synthesized antibacterial HAP-alginate composites with chlorhexidine and studied their swelling characteristics and chlorhexidine drug discharge for dental applications. Lin et al., [110] study the capability of Mg ion release in the prepared poly(lactic-co-glycolic acid)-MgO-alginate core–shell microspheres. The 3-(trimethoxysilyl) propyl methacrylate coated microspheres when cultured with pre-osteoblasts cell lines exhibited a 30% elevated MTT assay compared with pure poly(lactic-co-glycolic acid) microspheres after three days. Also, the *in vivo* studies performed on Sprague-Dawley female rats proved that after 8 weeks nearly 75% of new healthy bone was observed in the alginate composite microspheres. Anita et al prepared HAP scaffolds using alginate as a structuring agent. Fig. 7 shows the HAP scaffold prepared using Alginate as a binder. It was the micro and macro porosity that was compatible with cell proliferation and cell regeneration and hardness compatible with cancellous bone [111].

In a recent study, 3D scaffolds were prepared using bio-inks made of Sodium alginate and sulfated alginate along with osteoblasts and BMP2 for delivery of BMP2. It was found that enhanced proliferation, osteogenesis was observed for the alginate composite [112]. Further, Catanzano et al., suggested that strontium customized alginate scaffolds were appropriate for use in bone tissue applications [113].

10.3.5. Chitin/Chitosan

Chitin is an ordinary natural polymer broadly originated from fungi and insect shells, on the other hand, chitosan (CS) belongs to a linear polysaccharide segregated from chitin [114]. The insignificant deacetylation of chitin through chemical or enzymatic hydrolysis results in the development of CS [115]. Analogous to alginate, CS has verified immense capability for use in nanomedicine and tissue engineering applications [116]. Nevertheless, the mechanical characteristics of chitosan-based scaffolds are always incomparable with those of ordinary bone [116]. Thus, incapable to sustain the load when used in load-bearing conditions in bone implantable devices. Furthermore, chitosan by itself is not osteoconductive and thus combined with biopolymers or bioactive nanoceramics such as SiO_2, ZrO_2, TiO_2, HAP, etc. that enhances mechanical potency and structural reliability of chitosan-based composites for bone tissue engineering applications [117–121].

10.3.6. Gum ghatti

In the food industry, Gum Ghatti (GG) is one of the plant-based gums, which is used as a dominant emulsifier. It is also been explored as a drug delivery agent and food additive. It has been utilized in the medical industry as a stabilizer and emulsifier, after been declared as a safe drug. GG-based drugs are found in countries like India and Sri Lanka. It is extracted from the bark of the Anogeissuslatifolia tree wound in the form

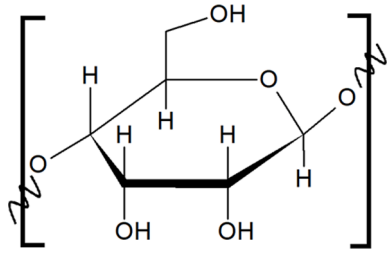

Fig. 8. The chemical structure of GG.

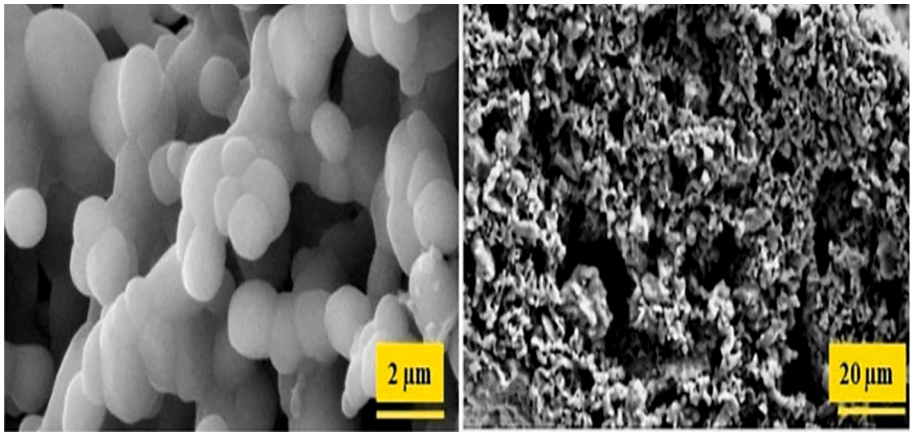

Fig. 7. HAP scaffold prepared using Alginate as a binder [111].

of lustrous mucilage. The chemical structure of the GG is shown in Fig. 8. This mucilage comprises elements like calcium, potassium, sodium, and magnesium salt; upon hydrolysis yielding *D*-xylose, *D*-galactose, *L*-rhamnose, *D*-mannose, *L*-arabinose, and *D*-glucuronic acid. Mittal et al. demonstrated successful incorporation of Fe_3O_4 in the polymer matrix of GG and acrylic acid-co-acrylamide based crosslinked for effective and efficient absorption of Rhodamine B dye from contaminated water, due to its high adsorption capacity [122]. Sharma et al. fabrication of GG/poly(methacrylic acid-aniline) hydrogel supported for uniformity of the network and ion dispersion with the cross-linked hydrogels when monitored by ion mass spectrometry chemical imaging technique [123].

The hydrogels exhibited a reduced amount of release in acidic and neutral media compared to basic media, signifying their suitability as drug transporter for drug deliverance in the lower gastrointestinal tract. Researchers have also prepared combined natural gum composite such as montmorillonite (MMT) composite matrices impregnated alginate-Arabic gum gel and further coated with alginate-ghatti gum suitable for flurbiprofen (FLU) delivery [124]. In recent times, Anita Lett et al. fabricated a HAP scaffold using a natural binder gum ghatti, the stereo zoom and FESEM image show the particle interconnected micro and macropores in the sintered sample. The examination Micro-CT images exhibited the overall porosity and its interconnectivity between the unsintered and sintered sample as shown in Figs. 9 and 10 respectively. The seeded MDCK cell lines on the samples supported cell proliferation and osteointegration to be used in bone tissue engineering applications [46].

10.3.7. Hyaluronic acid

Another group of the anionic copolymer is Hyaluronic acid (HA), comprising of β-1,4-*D*-glucuronic acid-β-1,3-N-acetyl-D-glucosamine units [125]. HA is commonly seen in connective tissues and neural and epithelial tissues [126]. Remarkably, —OH and —COOH acid groups has the potential to combine HA with other compounds, thus making it extremely biocompatibility and biodegradability [126,127]. In the medical field, it is used for the management of many pathological syndromes such as arthritis. Many researchers have used HA for tissue engineering and local drug delivery applications [124,128].

10.3.8. Tamarind gum

Tamarind gum (TaG) was originally separated from the endosperm of Tamarindus indica Linna, with branched and side chains. The foremost major chain that resides is β-D (1-4)-linked glucopyranosyl units and subsidiary links with xylopyranosyl unit-linked main link. The taG has widespread use in pharmaceuticals because of its biocompatibility [129–132]. Sangnim et al. systematically designed clindamycin-integrated nanofibrous scaffolds comprising of enriched polyvinyl alcohol (PVA) blend enriched with TaG by the use of electro-hydrodynamic dissolution [133]. The potential antibacterial behaviour of GaT enriched polymeric nanofibrous scaffolds incorporated with less than 2.5% of clindamycin exhibited potential antibacterial activity against Staphylococcus aureus.

10.3.9. Gum Arabic

Gum arabic contains a multifaceted mixture of glycoproteins and -polysaccharides principally composed of arabinose and galactose. It finds application in the food industry as a principal constituent in conventional lithography and a variety of industrial applications. Hadavi M et al prepared HAP/Gum Arabic nanocomposite using the freeze-drying

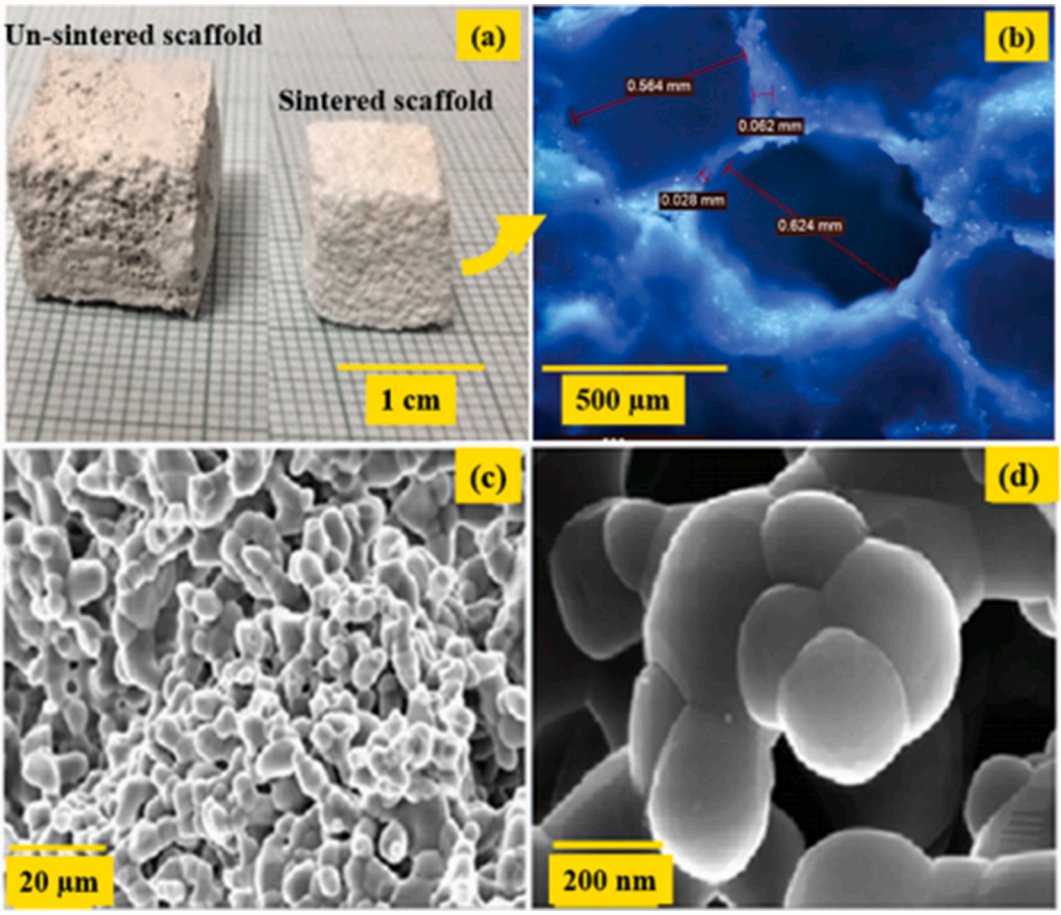

Fig. 9. (a) Light photograph of the un-sintered and sintered scaffold and (b) stereo zoom optical microscopic image of the sintered HAP scaffold. FESEM images of sintered HAP scaffolds at two different magnifications of (c) 20 mm and (d) 200 nm [46].

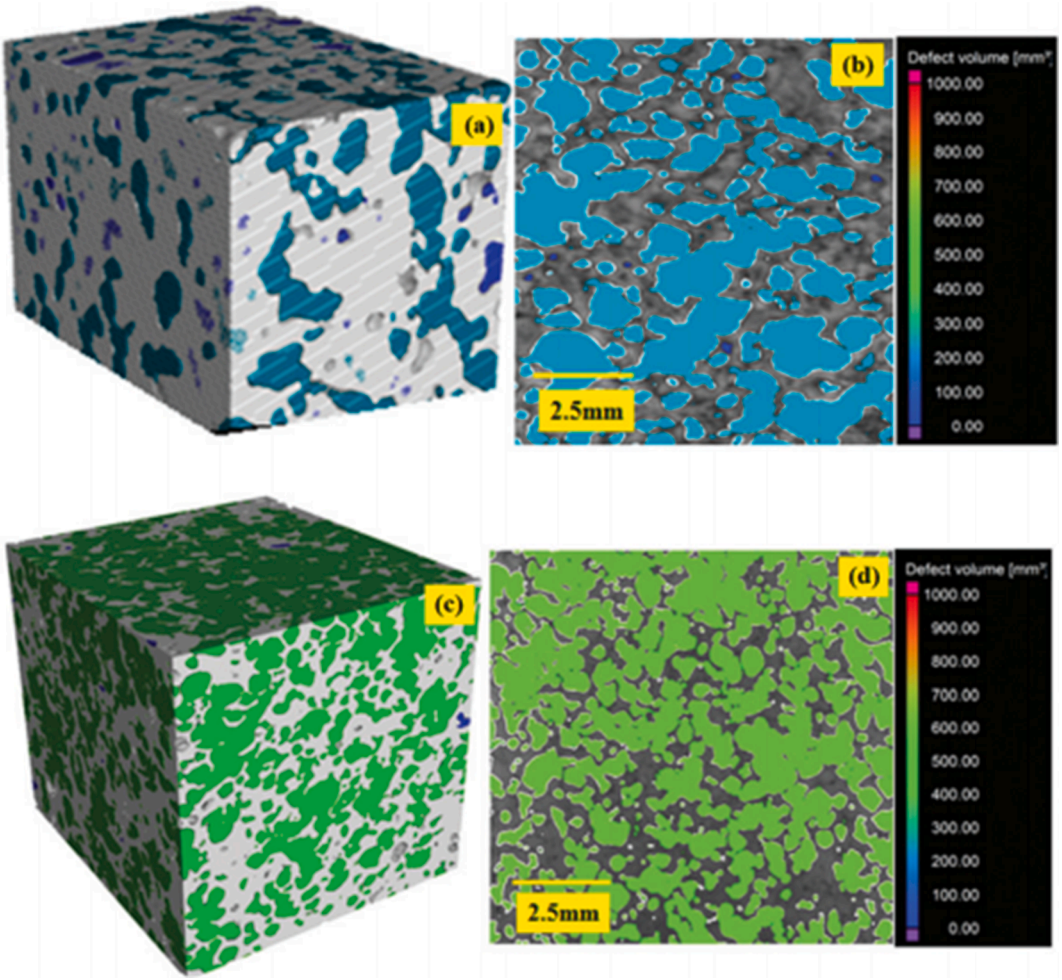

Fig. 10. Micro-CT images representing the porosity and pore interconnectivity of the HAP scaffolds before (top) and after sintering (bottom), as (a and c) 3D images, and (b and d) 2D cross-sectional views [46].

technique. His research outcomes confirmed that the nanocomposite had agreeable biocompatibility well-matched to the natural bone. It was found that the mechanical characteristics and osteoconductive properties of the scaffold can be tuned by modulating the mineral constituent. Scaffolds prepared using a 40:50 ratio of HAP/Gum Arabic concentration possessed enhanced highest biomineralization when immersed in SBF, as well as increased compression strength [134].

10.3.10. Cashew gum

In recent years cashew gum (CG), among the other biopolymers, has also achieved importance in its anti-inflammatory and healing properties [135]. The CG belongs to the family of polysaccharide chiefly encompassed of galactose, *D*-glucose, glucuronic acid, arabinose, and rhamnose [136,137]. Due to its viscous nature, CG can be used as a coating mediator [138,139]. Recently, Beserra et al. emphasized the use of HAP scaffold reinforced by biopolymers, such as CG, and GG, as a binding agent in the patterning of well-organized composites, scaffolds. The synthesized scaffold is shown in Fig. 11. Compressive strength in the order of 19.19 MPa was attainable analogous to the cancellous bone's strength along with adequate biocompatibility required for the applications of bone tissue engineering [140].

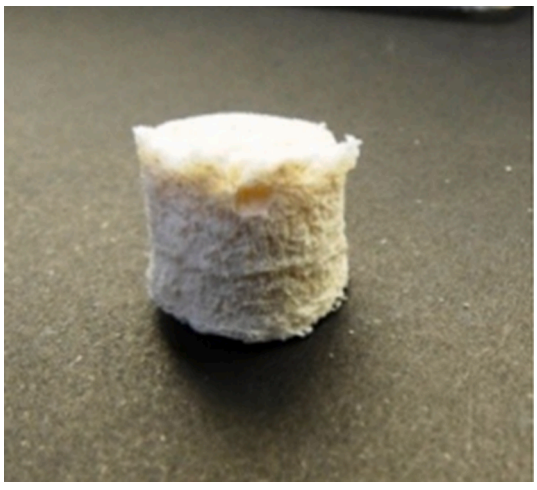

Fig. 11. HAP scaffold using a freeze-drying technique using CG and GG.

10.3.11. Guar gum

Guar Gum (GGu) is an industrial gum used for enormous purposes. It is a different form of water-soluble polysaccharide that acts as a perfect gel for particles of ceramic. It has the highest molecular weight amongst the water-soluble polysaccharides limiting from 0.2 million to 5.0 million renderings a high viscosity. It is considered in ceramic displacements to render good quality at low concentrations. The structure of GGu is shown in Fig. 12. A greater quantity of ceramic solids is needed for minimal binding concentrations. Post-extrusion problems are reduced [141]. Since, GGu is non-toxic, biocompatible, and biodegradable, it has manifold uses in bioceramics and also in the cell-loading

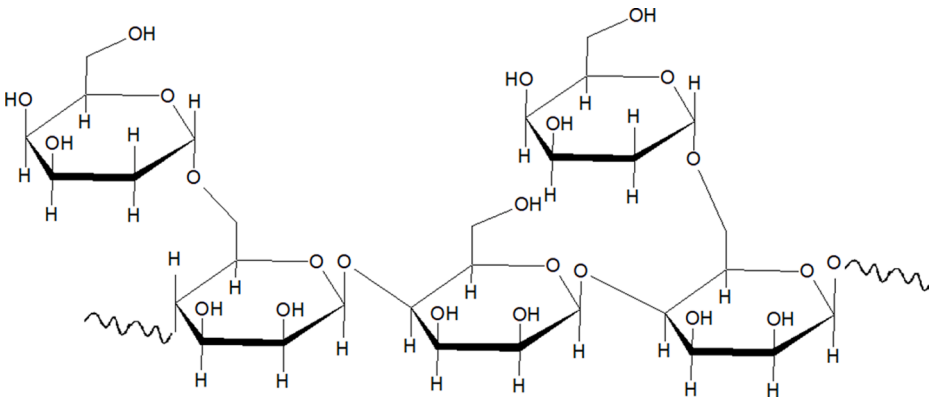

Fig. 12. The chemical structure of GGu.

process. When GGu is chosen as an agent, thermal gelation remains stable and enables it to develop within the ceramics.

The consequence of using GGu in collagen-based biocomposites highlights that composites with adjustable pore size, are best for cell growth and can be accomplished by changing the GGu concentration, which can be useful in the case of biomedical application [142]. Auddy et al., have developed a nanocomposite of silver nanoparticles dispersed in the polymeric matrix of NAg-GGAA for greater wound healing effectiveness [141]. Also, studies reveal porous honeycomb structures using Carrageenan-GGu material applicable as a scaffold and have been accomplished as wound curing material for clinical applications [143]. Carboxymethylated GGu explicated the opportunity of embedding with EDA for drug delivery and other biomedical applications particularly for wound therapy [144]. The fabricated scaffold was originated to form spongy bone architecture with interconnected micro and macropores as shown in Fig.13 [145]. The effect of sintering temperature concerning porosity and the mechanical property was analyzed. The scaffolds sintered at 1100 °C were found to be compatible with phase purity as well as mechanical property and thus can be used for replacing bone (e.g. cancellous bone) [145]. The preparation methods, effects of process parameters (features of the HAP, temperature condition, coating technique, etc.), properties, advantages, disadvantages, and various applications of the polymer-based HAP scaffolds are summarized in Table 2.

11. Applications

HAP is suitable for various applications in the biomedical field, particularly for bone substitution, as HAP is known to have good bioactivity, biocompatibility, mechanical strength, porous structure, and also osteoconductive, osteoinductive, and osteointegration properties.

11.1. Hard tissue repairs

HAP is widely utilized in the repair of hard tissue such as human bone and tooth for more than 40 years. Calcium is the major component in the vertebrate bones and teeth in the form of hydroxyl-deficient and carbonate-rich apatite with a Ca/P ratio lower than 1.67. The mechanism showing the action of calcium, phosphate, and water in the calcification of HAP is shown in Fig. 14. Moreover, the chemical formula and properties of synthetic HAP are similar to those of the biological apatite that makes up 70% of bones [175,195]. HAP uses includes (i) as granules or powders in bone and tooth decay (ii) as one of the constituents in bone cement and toothpaste (iii) tiny and removable implants in the middle ear (iv) temporary scaffold for host cell infiltration and new bone formation at non-load-bearing sites (v) as bioactive and biocompatible metal implant coatings in dental implants and hip prosthesis (vi) mechanical strengthening and bioactive phase in a polymer - bioactive ceramic composite [188,196]. It is found that synthetic HAP grafts amalgamate with the neighbouring host bone and helps in the progress of development of a new bone, which results in the bonding of a new bone and also in the improvement of damaged bone tissue. The more recent development in the field of HAP synthesis managed to produce nano-HAP using more environmentally responsible techniques. The nano-HAP was found to have improved sinterability and the scaffold can be produced with higher density, toughness, mechanical strength, bioactivity, and biocompatibility. Due to its improved characteristics and nano size, nano-HAP has more uses and also better functionality as a bone substitute [197]. One of the important functions of nano-HAP is to coat the dental bone implant as the nano-HAP can reduce implant rejection and improve the integration of the implant [148,198].

Also, biological activities including cell growth and differentiation, and bone regeneration are closely associated with HAP materials' porosity and micropore size, crystal shape and size, crystallinity, and ion substitution [199]. For example, tooth enamel consists of needle-like apatite nanocrystals and after a substantial mineral loss, the enamel is

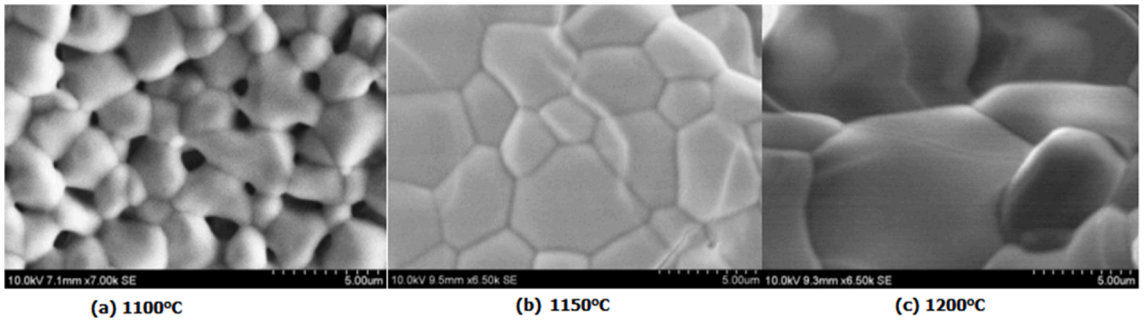

Fig. 13. FESEM of HAP scaffold sintered at (a) 1100 °C, (b) 1150 °C, and (c) 1200 °C [145].

Table 2
Summary attributes of the polymer-based HAP scaffolds.

Method	Features of HAP	Temperature	Surface modifying agent	Techniques used	Coating technique	Advantages	Disadvantages	Applications	References
Hydrothermal	Brittles with length of 20–30 mm and 0.1–1 mm width	80–400 °C	Hydro stearic acid	Direct reaction	Dip coating	Requires high pressure	Size and shape are not controlled	Drug delivery systems	[146,147]
	Forms hexagonal and narrow rod-shaped		Oleic acid	Direct reaction		Environmentally friendly	Not preferred for all the materials.	Control release of drugs	[148–150]
			Decanoic and hexanoic acids	Direct reaction	Sputter coating	Single-step process	High-pressure equipment	Bone grafts and implants	[151–154]
Sol-gel	Produces a size of 20–50 nm and the cost of precursors is quite high	65–600 °C	Silanes	Coating		Includes molecular-level and high reactivity reaction	Expensive method	Bioactivity and compatibility can be improved on coating	[155–162]
			Polyacrylic acid	Coating	Pulse laser deposition		Moisture sensitive	Coatings on the metal surface along with HAP	[151,163–166]
			Γ-methacroyloxytrimethylsilane	Coating				Gain a high degree of crystallinity	[167]
Wet chemical	Biphasic rod-like structure is formed	140 °C	Serum	Grafting	Electrophoretic deposition	Simple step process	Acquires exceptionally low yield	Stoichiometry	[168–172]
						Requires extremely low temperature	Isotropic etching	Porosity and good adhesion to the substrate.	[173–175]
			Vinyl phosphoric acid	Grafting	Electrostatic spraying and plasma spraying	High product yield and easy to control	Depends on the reactant solubility and precipitation rate	Scaffolds for tissue engineering	[176]
			Ethylene glycol methacrylate phosphate, *L*-phenylalanine	Grafting, polymerization		pH, temperature, morphology, size, and shape			[177–185]
Biomimetic deposition	Bone-like apatite layer is formed	37 °C	*N*-carboxy anhydride	Polymerization	Layer by layer coating	Nucleation process is performed by simulated body fluid	Calcination process requires high temperature	Bone tissue engineering	[177,183–185]
Precipitation method	Nodular shape HAP is formed	100–1300 °C	Potassium dehydrogenase phosphate	pH 9–10		Simple technology, low cost, large scale possible	Results in poor uniformity and agglomeration of the particles	Bone implants	[186–194]

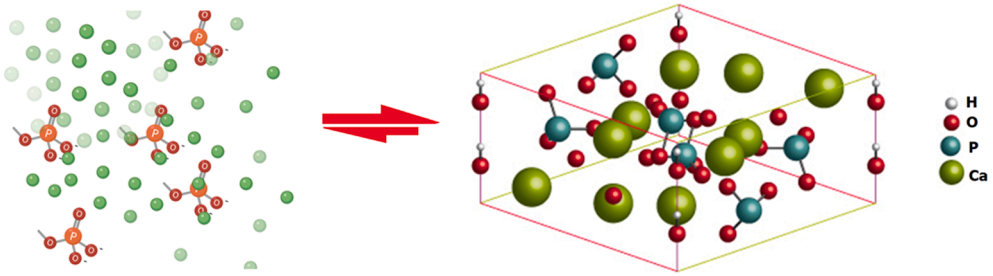

Fig. 14. Mechanistic action of calcium, phosphate, and water in calcification mechanism of HAPs.

rarely able to self-repair [200], suggested that 20 nm-sized HAP is superior to other restorative material that has been used to date to repair eroded enamel perfectly. To induce the remineralization of the enamel surface, the nano-HAP can be strongly adsorbed on enamel surfaces. HAP nanocrystals also have been identified to play a superior bioactive role in facilitating cartilage regeneration [201]. Incorporation of nano-HAP in the PLGA scaffold was found to better promote chondrocyte adhesion and proliferation enhances mechanical properties of regenerated cartilage, and enhance antifriction properties, thus have excellent cartilage regeneration capabilities [202].

11.1.1. Bone graft

The bone graft fabrication by tissue engineering strategy utilizes cell, cell derivatives, and bioactive components to improve the bioactivity of the pure HAP or HAP composite scaffold and to promote bone regeneration [203]. A schematic representation of bone regeneration is shown in Fig. 15. HAP has a high potential to function as a temporary bone graft that promotes bone reunion as HAP is chemically similar to the main component of bone and also HAP scaffold can be fabricated to have similar mechanical properties as natural bone. The osteoinductive and osteointegration properties of HAP facilitate the formation of new bone by the host and complete regeneration of bone following the resorption of the HAP [204]. HAP particles found in composite scaffolds can function as both bioactive and mechanical components of reinforcement when dissipated into a biopolymer matrix [26]. Furthermore, the HAP can be combined with other ceramic materials, cells, and cell derivatives to induce, guide, and enhance bone regeneration. A study by Shamsuddin et al. utilized beta-tricalcium phosphate and HAP (β-TCP/HAP) granules combined with autologous bone marrow-derived stem cells and fibrin to induce bone formation and alveolar ridge restoration in the monkey model[205]. The study showed new bone formation around the implant and new bone integrated with the native bone . The hierarchical structure of bone is represented by different levels of an organization [206].

11.2. Drug/gene/protein carriers

Increasing research is being performed to use HAP as the drug carrier, especially using nano-HAP particles [87,94,141,207]. The rough surface of HAP, presence of hydroxyl group, and combined with the presence of two different charge planes on their surface, C-sites, and P-sites, promote the adsorption of proteins to HAP [208]. Furthermore, the high surface to volume ratio properties of HAP nanoparticles, similar to any nanoparticle, made HAP suitable for loading and delivery of various drugs such as growth factors, hormones, antibiotics, and anticancer drugs [209]. Antibacterial properties of HAP nanocomposites as shown in Fig. 16 [210]. Nano-HAP loaded with doxorubicin was previously used in combination with HA (referred to as DOX/HAP-HA) to increase tumor targeting and the study successfully targeted mitochondria and nucleus of tumorigenic cells with satisfactory drug loading efficiency (Fig. 17) [211]. Besides conventional drug delivery, HAP is also found to have the potential to deliver DNA, siRNA, and miRNA for gene therapy [212]. The previous study has successfully delivered nucleic acids to mesenchymal stem cells both in monolayer and on scaffolds using miRNA loaded collagen-HAP nanoparticles and no cytotoxicity was observed [213]. Medicines transmitted from nanoscale elements may act uniquely as opposed to those transmitted in an ordinary or customary frame [210] (Fig. 16).

HAP materials are also favoured as carriers for drug and gene delivery due to its superb biocompatibility, adjustable physicochemical properties (e.g., porous structure, size, shape, and surface composition), pH-dependent dissolution, low toxicity, excellent storage stability, cheaper production cost, stable against microbial degradation, etc. [214]. The degradation rate of HAP appears to increase with the pH change from alkaline to acidic conditions, which accelerates the release of drug molecules from the HAP surfaces. To overcome HAP's disadvantage in drug carriers, porous-structured materials were manufactured [215].

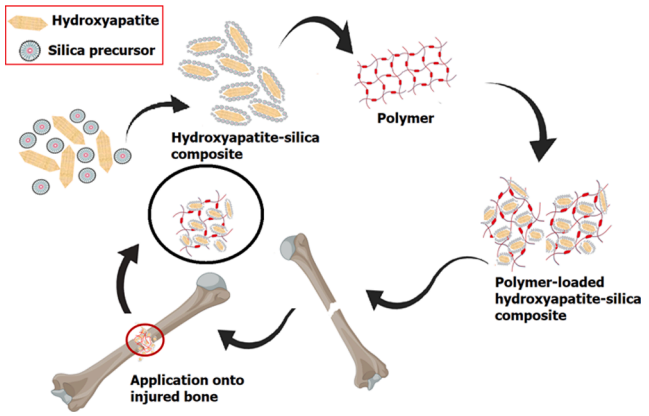

Fig. 15. Tissue regeneration on the injured bone.

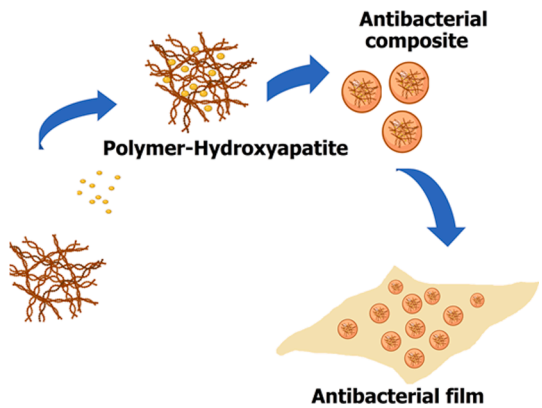

Fig. 16. Antibacterial properties of HAP nanocomposites.

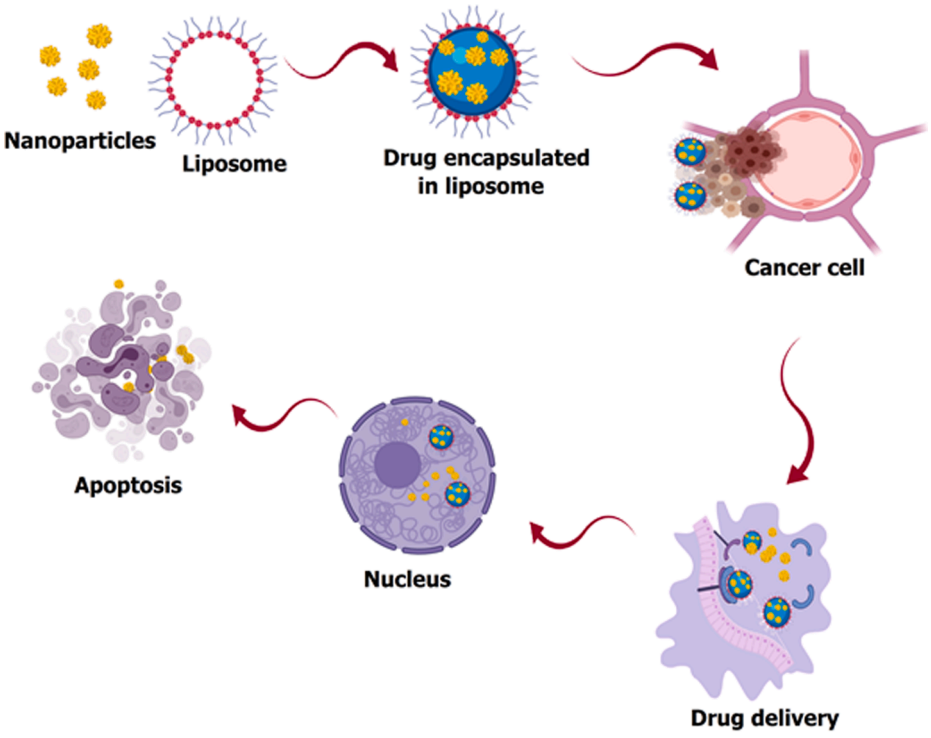

Fig. 17. Targeted antitumor drug delivery to the cell nucleus and mitochondria using DOX/HAP-HA.

12. Conclusions and future directions

The advances in the field of tissue engineering have increased the utility of HAP in various biomedical applications. The biological and physicochemical properties of HAP that are adaptable to the human physiological environment made it a suitable biomaterial for hard tissue engineering a long time ago. The evolution in various fabrication techniques, production of synthetic HAP, and also the development of various HAP composite materials with variable properties have expanded the horizon of HAP usage in the biomedical field. However, there is some weakness of the HAP material, such as lower mechanical strength compared to native bone, difficulties in regulating the biodegradation to enable bone formation by host tissue, and lack of osteoinductivity properties that need to be addressed to enable wider usage of HAP in the biomedical field.

Besides that, it has to be bioresorbable or bioactive with adequate mechanical property to confirm loading performance that might exist at the implanted site. A bioactive material draws out a definite biological response at the surface of the biomaterial, which results in the development of new bonds among the bone tissues and the material, whilst a bioresorbable material slowly degrades with time along with natural tissue replacement. With the consideration that the main compositions of the natural bone are HAP crystals and collagen fibers, the nano-HAP simulates excellent characteristics like bioactivity and biocompatibility that are essentially significant for bone development. Therefore, the organic/inorganic composite materials hold high potential in bone tissue engineering applications. Despite that a wider range of scaffolds have been developed through a direct combination of various active additives still, the produced scaffolds lead to uncontrolled homogeneity in the polymer matrix.

13. Data availability

All relevant data are within the paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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