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Review

Polylactic acid (PLA): Properties, synthesis, and biomedical applications – A review of the literature

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ABSTRACT

This comprehensive review is an in-depth analysis of polylactic acid (PLA), an increasingly important biopolymer due to its wide-ranging applications and sustainability features. PLA's physical, thermal, and mechanical properties are closely linked to its molecular distribution, mass, and stereochemistry, allowing it to exist in amorphous or semicrystalline states. The controlled polymerization of different optical monomers enables the creation of different types of PLA with distinct properties. To address PLA's inherent hardness limitation, researchers are exploring blends with stereo complexes like PLLA/PDLA, leading to improved mechanical and thermal properties. PLA's moldability supports its versatility in various forms, from nanoparticles to resorbable sutures. Focusing on composite materials, the review discusses the use of PLA in reinforcing synthetic and natural fibers to obtain composites, and in the production of micro- and nanoparticles. The incorporation of fibers, such as wood, cotton, and carbon-based synthetics, significantly influences the composite's mechanical properties. Additionally, the rise of nanoscale fillers, including clays and nanoparticles, has offered cost-effective solutions for enhanced material performance. Synthesis methods for PLA encompass direct polycondensation and ring opening, with the latter preferred due to improved control of polymerization. The degradation behavior of the polymer which, together with its biocompatible properties and eco-friendly production methods, makes PLA a potential material for biological applications. The innovative features, obtained by the bibliometric map generated with the VosViewer software from Scopus database, highlights the role of PLA in the biomedical field, in particular for tissue engineering by improving healing rates and, as well as for implants and prosthetics.

1. Introduction

Polymers have revolutionized the way we deal with the applicability of materials, being these of great versatility and diversity, that make them suitable to be used in equipment, tools, electronic devices, cosmetics, drug formulations, and in the biomedical field. The wide range of polymers' applications is explained by the multiple structures and sizes of the carbon chains, which impact directly their mechanical and physicochemical properties. Thus, different types of polymers can be used to satisfy diversified needs. The selection of the most adequate polymer depends on a detailed study of its properties, to ensure that its characteristics match the designed purpose. For example, surgical implants must resist fatigue and at the same time degrade over time so that there is no need for surgery to remove them [1]. The recent replacement of materials such as glass, wood, and metal with polymers is a reality. Due to their low cost, malleability, and ease of manufacture, polymers are proving to be more economically viable than other materials [2].

However, due to the global awareness regarding the life cycle and non-renewable origin of most polymers (usually from petroleum), the large-scale production of polymers results in disposal problems, in particular for polymers that require thousands of years to decompose. Therefore, more research is necessary to minimize environmental

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impacts [2–5]. Thanks to recent advances in biomaterials, such as biodegradable and bioresorbable polymers, together with the development of new bio-fabrication techniques, biopolymers have attracted great attention from consumers and manufacturing markets, being applied not only in plastic bags but also in medical devices. As a result, industries have been looking for new sustainable means of production to meet the market's growing demand for green polymers, making polylactic acid (PLA) a great alternative [6–8].

PLA is an aliphatic polyester composed of blocks of lactic acid, or 2-hydroxypropanoic acid. The building block for the synthetic PLA polymer is lactic acid, which was isolated the first time by the Swiss chemist Scheele in the 1700s, and its first biomedical application was in the repair of mandibular fractures in dogs [9]. However, because of its high cost and low availability, the use of PLA was firstly limited to medical applications, but currently high molecular weight PLA can be processed by extrusion, injection moulding, blow moulding, electrospinning and thermoforming. PLA also offers similar thermal, mechanical, optical and barrier properties compared to commercially available polymers, such as polystyrene (PS), polypropylene (PP), and polyethylene terephthalate (PET), thus widening its use for a range of other applications [3].

PLA is extremely versatile, and can be moulded into several structures, including nanoparticles, films, scaffolds, rods, sutures, and micelles. Its industrial uses include both durable consumer goods and perishable goods, such as flexible films and rigid packaging, cutlery, cold drink cups, bottles, clothing and staple fibers, injection moulded products, and extrusion coating. However, PLA medical applications are in high demand – in 2014 the expenditure of the Unified Health System in Brazil with prostheses exceeded R$ 1 billion, of which R$ 730 million were spent on cardiovascular devices and R$ 210 million on orthopaedic devices. Considering this growing interest in the health sector, there is a need for research to promote the development of new technologies that facilitate and improve the use of PLA [2,6].

Thus, this review discusses the advantages and limitations of PLA, since it is one of the most commonly used biopolymers in the biomedical field. This paper addresses the PLA state of the art, routes of synthesis, and physicochemical properties that enable a great deal of applications of PLA in the biomedical field. It is noteworthy that PLA via ring opening polymerization (ROP) presents interesting physical properties that can be used more efficiently in the medical field, while some applications are also presented (tissue engineering, sutures, prostheses, drug delivery systems).

The large majority of known polymers are obtained from non-renewable petrochemical materials, e.g., polyethylene terephthalate (PET), polyvinyl chloride (PVC), polyamide (PA), polypropylene (PP), polyethylene (PE), polystyrene (PS). The growing commercial interest in biopolymers like PLA is a result of public concerns about the environment, climate change, and the depletion of fossil fuel supplies. In addition to being derived from renewable sources and being easily and completely biodegradable, the PLA also sequesters significant amounts of CO2 and reduces landfill volumes [10], while synthetic polymers have degradation periods that can last centuries (Table 1). Biopolymers, on the other hand, are polymers synthesized from renewable natural sources and/or can be synthesized by biological systems (animals, plants, microorganisms) or obtained by chemical synthesis from biological materials e.g., oils, natural fats, starches or sugars [11].

Table 1
Degradation time of some polymers.

Polymers	Degradation Rate	Refs.
Polycaprolactone (PCL)	> 24 months	[12]
Polyethylene (PE)	100 to 400 years	[13]
Polyethylene terephthalate (PET)	400 to thousands of years	[14]
Polylactic Acid (PLA)	1 week to 24 months	[15]
Polypropylene (PP)	30 years	[16]
Polystyrene (PS)	> 400 years	[17]

With the aim of reducing the consumption of petroleum products, the biopolymers market is gaining ground over polymers of non-renewable origin, precisely because of their sustainable and eco-efficient portfolio. Biopolymers are more competitive over petroleum-based plastics in terms of cost and performance. Biocomposites are obtained from the reinforcement of biopolymers or synthetic polymers with biofibers, and can be a viable alternative over other composites reinforced by glass fibers [11]. Directly extracted polymers are those obtained from natural materials, mostly from plants, as happens with polysaccharides (e.g., starch and cellulose), and proteins (e.g., gelatin, casein, silk and wheat flour). Chemically synthesized polymers are those obtained from renewable biodegradable monomers such as poly(glycolic acid), poly (lactic acid), and their biopolyesters. These are polymerized from lactic/glycolic acid monomers obtained from the fermentation of carbohydrate feedstock. Polymers can also be produced by genetically modified microorganisms or bacteria, such as bacterial cellulose, xanthan, polyhydroxyalkanoates [11].

Biodegradable polymers can degrade under certain conditions of temperature, humidity and the presence of certain microorganisms. The American Standard for Testing and Methods (ASTM) and the International Standards Organisation (ISO) describe degradable plastics as those that are capable of undergoing significant modifications in their chemical structure under specific environmental conditions, in which may result in the loss of physical and mechanical properties that can be evaluated using standard approaches [18].

The term biomaterial was defined at the 1982 Consensus Conference on Biomaterials for Clinical Applications as any material (other than a bioactive ingredient) or a combination of materials, of natural or synthetic origin, that can be applied for an indetermined period of time, as a whole or in part, as part of a system that treats, increases or replaces any function, organ or tissue of the organism, with the purpose of maintaining or improving the quality of life of the individual. Biomaterials can also be defined as any body or object that is in continuous or intermittent contact with body fluids, even if it is outside the body. Thus, pins and external fixation plates are not considered biomaterials, whereas scalpels, blades and other surgical instruments are. Some synthetic polymers used in tissue engineering are poly (lactic acid) – PLA, poly (glycolic acid) – PGA, poly (ethylene glycol) – PEG, and the natural derived are collagen, hyaluronic acid, alginate, agarose, fibrin, etc. [19]. Several applications of biomaterials in tissue engineering have been reported (Table 2).

2. Chemistry, industrial production and physicochemical properties of PLA

Lactic acid (LA), or 2-hydroxypropanoic acid or α-hydroxypropanoic acid, is the only monomer present in PLA and can be obtained by fermentation or chemical synthesis, its structure is shown in Fig. 1. It has two forms of active optical configurations, the stereoisomers L (+) and D (-) [3].

Bacterial fermentation is used to produce LA monomer, which can be

Table 2
Applications of various polymers used in tissue engineering (modified after [19]).

Application	Polymer used
Skull repair	PE
Intraocular lenses	PMMA. HYDROGELS
Ortho laryngological implants	PET, PFTE
Maxillofacial reconstruction	PE, vinyl resin
Dental reconstruction	Vinyl resin, PMMA
Filling of alveolar parts	PLA, PGA, PU, PDMS
Periodontal cavity reconstruction	Vinyl resin
Pericutaneous access devices	PE, PET, PTFE
Artificial heart valves	PET, PU, PTFE
Femoral thigh repair	PMMA

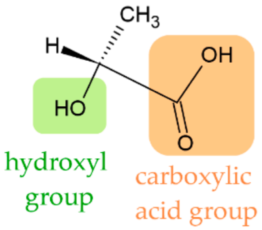

Fig. 1. Bifunctionality of lactic acid (modified from [20], with permission from Elsevier).

either homofermentative or heterofermentative depending on the type of Lactobacillus used in the process [21]. The heterofermentative Lactobacillus spp. produces less than 1.8 mol of LA from 1 mol of hexose, and resulting from the fermentation process significant amounts of other metabolites (e.g., acetic acid, glycerol, ethanol, mannitol, and carbon dioxide). On the other hand, in the homofermentative method, from 1 mol of hexose results an average of 1.8 mol of LA, with lower levels of other metabolites, meaning that each 100 g of glucose will result in more than 90 g of LA. Since homofermentative Lactobacillus spp. produces higher yields and lower levels of by-products, this method is more widely used in industry compared to the heterofermentative method. When LA is used in the pharmaceutical and food industries, it must be purified by distillation. To reduce the levels of calcium hydroxide and sulphuric acid by-products obtained from the process, NatureWorks LLC adopted a lower pH approach to produce LA, resulting in lower calcium sulphate production [3].

The industrial production of LA is carried out by fermentation rather than by chemical synthesis, mainly because this synthesis has many limitations that include the high production costs and the inability to produce only the desired L-lactic acid stereoisomers [22]. LA is a hydrophilic monomer, soluble in water and water-miscible organic solvents, and insoluble in other organic solvents. It is also commonly used in the food industry as a flavouring, pH buffering agent, acidulant and as bacterial spoilage inhibitor. In pharmaceutical and cosmetic formulations, LA finds several applications as well, e.g., in lotions, humectants, topical ointments, anti-acne dispersions, parenteral solutions [11].

The relevance of polylactic acid (PLA), shown in Fig. 2, began with the first synthesis by Wallace Hume Carothers in 1932, using a manufacturing process patented by DuPont in 1954. Carothers described the production of low molecular weight PLA through the heating of lactic acid under vacuum, following the removal of condensed water [23]. In the USA in 1974, PLA was combined with polyglycolic acid (PGA) to obtain a material for suturing and branded as Vicryl [22]. This polymer of biotechnological origin is classified as an aliphatic polyester, rigid thermoplastic, semi-crystalline or amorphous. It is insoluble in water, yet biodegradable, biocompatible, bioabsorbable and is recognised as safe by the Food and Drug Administration (FDA) [23,24].

The advantages of producing PLA over the other biopolymers result from the use of renewable sources in the fermentation process obtaining the lactide monomer from lactic acid. Besides, the ability to recycle by hydrolysis or alcoholization back to lactic acid, the possibility to fix a significant amount of carbon dioxide, its potential use in the production of hybrid paper and biodegradable plastic packaging, the reduction of landfill volumes, the use of leftover bagasse in industry, and the customization of physical properties through composites, increases the industrial interest in this polymer [22].

Because of its competitive cost and eco-friendly environmental footprint, the production of PLA is being increasingly growing for a range of industrial uses. The main method used to produce lactic acid monomer is bacterial fermentation of carbohydrates, a process used by NatureWorks LLC and Corbion®, the world's two largest producers of PLA [26], whereas the chemical synthesis encounters several limitations, that include the yield of production, the high costs and the inability to obtain the L-LA isomer only [3]. Other PLA manufacturers is presented in Table 3. The physical, mechanical and thermal properties of polylactic acid depend mainly on the molecular distribution and mass, and also on the composition. For example, depending on the stereochemistry, it can be amorphous or semi-crystalline in the solid state. It is only possible to generate a polymer with different properties by controlling the polymerization of different optical monomers, resulting in differentiated polymers.

One limitation of PLA is its hardness, so researchers are currently trying to blend PLA with other stereocomplexes such as PLLA/PDLA, which are the most common types, both synthesized by ring-opening (ROP). This blend improves the mechanical and thermal properties of PLA-based materials, besides their resistance against hydrolysis, due to the strong interaction between the sequences of L-lactyl units and D-lactyl [10]. Tsuji et al. (1991) [28] showed that the equimolar blend of PDLA and PLLA produces more resistant stereocomplex against high temperatures, with the increase of the melting point of 50 °C ($T_m = 230$ °C) compared to PLLA alone, indicating that this complex could be used in high performance applications [10,28].

With regard to the mechanical properties, PLA can be compared to polyethylene terephthalate (PET), as it has higher modulus and strength than other polyesters, and it has two active optical forms, PDLA and PLLA, the latter being the most important [10]. PLLA is a semi-crystalline, optically active, transparent hard solid with a crystallinity of approximately 37 % (depending on the molecular weight and polymerization process), a melting temperature (Tm) between 170 and 183 °C, a glass transition temperature (Tg) between 55 and 65 °C, and a

Table 3
List of the largest PLA producers (modified after [27]).

Enterprise	Location
Futerro (Galactic/Total)	HAD
Nantong JiudingBiologic	China
Shenzhen Bright China	China
Shanhai Tong-Jie-Liang	China
Zhejiang Hisun	China
Purac / Corbion	EU/ Thailand
NatureWorks LLC	USA / Thailand
Pyramid	Germany
Teijin	Japan

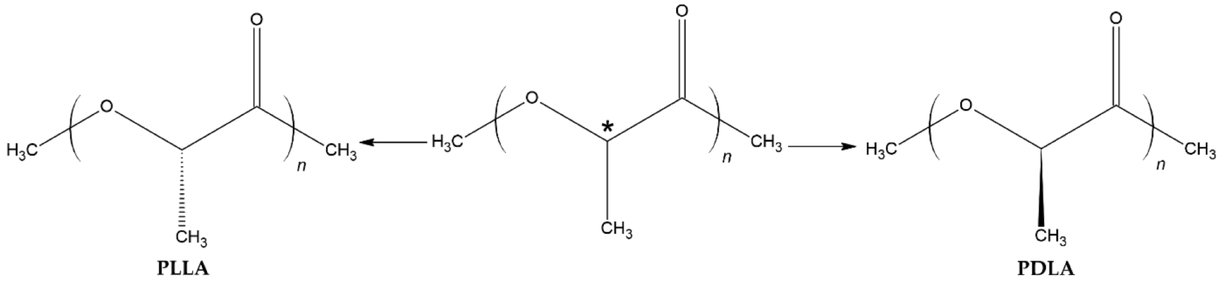

Fig. 2. Chiral PLA molecule. The carbon with an asterisk is chiral carbon (modified from [25], with permission from Elsevier). (PDLA, D-lactide; PLLA, L-lactide).

tensile strength of 45–70 MPa. PDLA is an optically inactive polymer, amorphous and with a much lower tensile strength [9]. Some physical properties of PLA are presented in Table 4.

PLA is extremely versatile and can be moulded into a variety of shapes, including scaffolds, sutures, dressings, screws and pins for bone fixation, controlled drug release, joint cartilage repair devices, muscle tissue, tracheal replacement, and others. As its production increases, operational costs decrease, allowing PLA to be used in a great deal of products [10,24].

A revolutionary application of PLA currently under investigation is 3D printing. 3D printers will greatly expand the possibilities in biomedical engineering, enabling numerous applications for PLA, which will be widely used as a temporary extracellular matrix for tissue engineering [9]. In a collaboration between Altran Italia, Thales Alenia Space and the Italian Institute of Technology for Use in Space, a portable 3D printer was developed using about 5.5 kg of PLA [29]. The properties of PLA, such as brightness and multicolour appearance, make it one of the first alternatives for 3D printing. High precision can be reached with PLA, as it exhibits less deformation than the materials usually used in this type of printing [3,30].

The most popular hydrophilic polymer for surface modification is recognised to be polyethylene glycol (PEG), which has been used to increase the hydrophilicity of PLA by the generation of the amphiphilic copolymer PEG-PLA. Table 5 gives some examples of polymers commonly used to blend with PLA.

A polymeric material having two or more distinct phases is known as polymer composite. The discontinuous phase (reinforcing phase) is dispersed in the continuous phase (matrix). The reinforcing phase can be composed of fibers and/or micro/nanoparticles. The main objective of adding a reinforcing phase to PLA is to adapt the properties (e.g., heat resistance, barrier properties, elongation at break, dimensional stability), and to reduce its costs. The aim is to overcome some of the limitations of PLA compared to polymers of fossil origin, such as low thermal stability and fragility. Since the properties of composites are mainly engineered by modifying the composition of the discontinuous phase, natural and synthetic fibers, micro- and nanofillers have been used to reinforce PLA [3].

Fibers with a higher length-to-diameter ratio have been proposed for PLA composites to widen the range of potential applications of this polymer. In order to obtain PLA composites with the desired properties, the dispersion and orientation of the fibers play a crucial role. The performance of the composites is strongly linked to the adhesion between the discontinuous and continuous phases, i.e., the adhesion between fibers and matrix of the polymer is instrumental for customizing the final properties. PLA is also being used in the production of new biobased compounds in combination with natural fibers, such as flax, cotton, hemp, as well as with wood. Synthetic fibers based on e.g., carbon or glass, are also being commonly used to reinforce PLA composites to improve their mechanical properties and tensile strength [3,10,31].

Table 4
Physical properties of PLA polymers (modified after [1]).

Property	Stereocomplex PLA	PLLA or PDLA
T_g (°C)*	65–72	58
T_m (°C)*	220–230	170–190
ΔH_m ($J.g^{-1}$)*	142-146	40–50
T_d (°C)*	-	310
Density ($g.cm^{-3}$)	-	1.25–1.29
Tensile strength (GPa)	0.88	0.12–2.3
Elasticity modulus (GPa)	8.6	7–10
Elongated at rupture (%)	30	4–7
Crystalinity (%)	PSLA: Amorphous	PDLA: semicristalline PLLA: 0–37

Captions: T_g = glass transition temperature, T_m = melting temperature, ΔH_m = melting enthalpy, T_d = decomposition temperature.

Table 5
Applications of polymers used in blend with PLA and their properties (modified after [1]).

Polymers	PLA stereo complex	PLLA or PDLA
Polyhydroxybutyrate (P3HB)	Packaging	58
Thermoplastic polyurethane (TPU)	Actuators, tissue engineering	170–190
Polycaprolactone (PCL)	Engineering tissues, grafts, artificial nerves	40–50. 93
Polyglycolic acid (PGA)	Soft tissue engineering	310
Polyethyleneglycol (PEG)	Drug Release, Scaffolds	1.25–1.29
Hyaluronic acid (HA)	Bone grafts, wound healing, tissue engineering	0.12–2.3
Chitosan (CHI) / PCL	Antimicrobial, dressings for haemostatic wounds	7–10
Lignin	Food packaging	4–7

Because of their low cost and environmentally friendly impact, micro/nano-sized fillers are also an option in the manufacture of composites. Inorganic fillers (e.g., hydroxyapatite, talc, carbon black, mica, and gypsum) are known for decades to reinforce the mechanical properties of polymers, even in small amounts. Currently, the addition of nanoparticles (e.g., nanoscale clay) is also a viable approach to significantly improve the performance of the polymeric material [3].

One way to improve the mechanical strength of polymeric matrices is to incorporate fillers such as montmorillonite clays. Besides improving these matrix properties, clays are known to have medicinal properties. When using this clay, it is necessary to use a biocompatible modifying agent, in which the interaction between the functional groups of the agent and the polymer will change the extent of intercalation of the polymer between the interlamellar spacing of the clay.

Fonseca et al. [32] showed that PLA nanocomposites containing 8 % TiO_2 and placed under UV irradiation obtained expressive antimicrobial and antifungal activities with reduction of *A. fumigatus* and *E. coli* of 99.9 % and 94.3 %, respectively, and thus concluded that this composite is extremely attractive for use in medical devices and/or food packaging with preservative properties.

3. Copolymerization of PLA

The most efficient and straightforward method for producing PLA-based products with a variety of characteristics is copolymerization. PLA crystallinity and melting point are reduced when a polyester backbone is added, but the copolymers' mechanical characteristics can be greatly changed, ranging from flexible, soft plastics to stiff, high-strength materials. For instance, poly(ε-caprolactone-co-lactide) (PCLA) is produced when ε-caprolactone and lactide copolymerize. Crystallinity is not seen when the LA concentration is larger than 30 % w/w and drops quickly from 73 % (PCL) to 31 % (PCLA containing 20 % w/w LA units). Additionally, the PCLA Tg exhibits a feature that is reliant on LA content; it increases as the LA unit content increases and thus properly fits the Fox equation [10].

3.1. PLA Polymerization

PLA can be synthesized from renewable resources such as sugarcane bagasse, potatoes and corn, and may play an important role in the future as a substitute for petroleum-based polymers. This synthesis takes place via two routes, direct polycondensation of lactic acid or by ring opening (ROP) of the lactide previously synthesized from lactic acid with metallic/bimetallic catalysts (Sn, Zn and Al) or other organic catalysts in an appropriate solvent (Fig. 3) [33].

Lactic acid can be used to produce PLA of different molecular weights, but high molecular weight PLA has greater commercial value. Three primary techniques of production of PLA include lactide formation polymerization, direct condensation polymerization, and direct

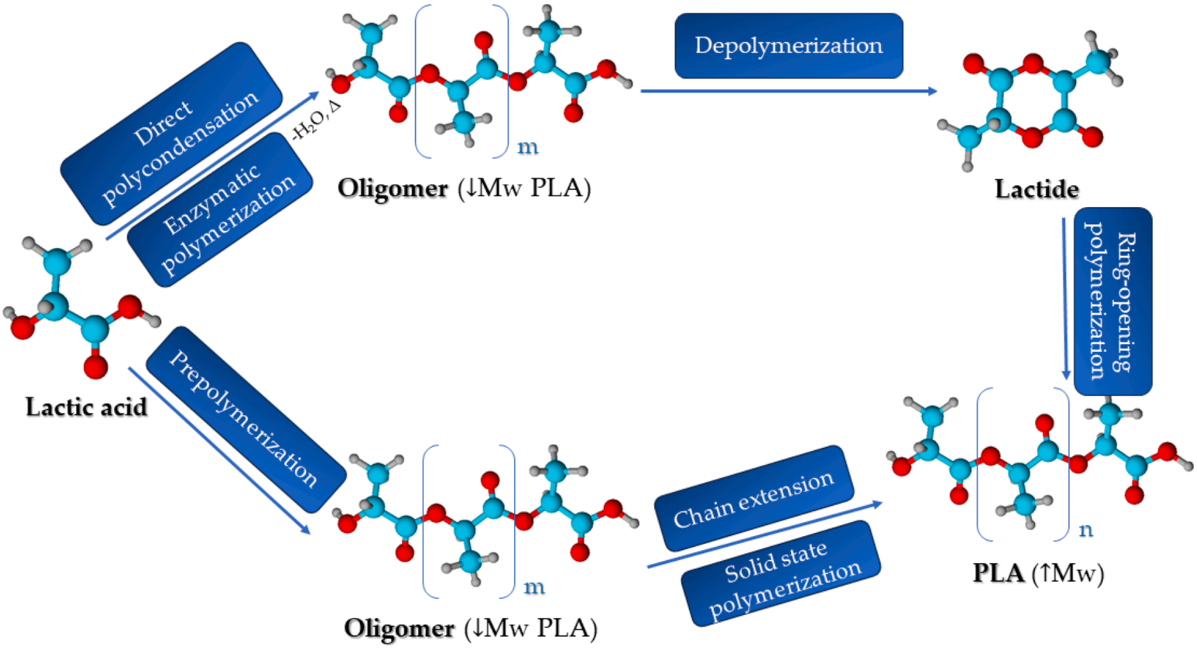

Fig. 3. Conventional routes to obtain the PLA (adapted from [34], with permission from Elsevier).

polycondensation in an azeotropic solution [3].

The most commercial approaches are those with better lactide conversion efficiency; instead of using polycondensation, a Sn(II)-based catalyst catalyzes the cyclic dimer from lactic acid to PLA through the ring opening (ROP). Both polymerization strategies rely on highly graded, high-quality polymeric lactic acid to produce high-yield, high-molecular-weight polymers [10,11].

Recent advancements in PLA synthesis emphasize a shift towards greener production methodologies. Particular attention is being paid to methods like enzymatic polymerization and neat polymerization. These techniques are alternatives to traditional approaches that involve hazardous solvents, thereby promoting a more environmentally sustainable production process. In addition to these methods, reactive extrusion emerges as a noteworthy optimization technique in PLA synthesis. This method seamlessly integrates polymerization with the melting process, offering a more economically attractive option. By combining these steps, reactive extrusion streamlines the production process, potentially reducing costs and resource utilization while maintaining a focus on sustainability. Overall, these innovative approaches represent a significant step towards a more eco-friendly and economically viable production of PLA [35–37].

3.2. Polycondensation

Polymerization by condensation occurs through intermolecular chemical reactions that involve more than one monomer. A low molecular weight by-product of this reaction is typically water, which is removed or condensed. The intermolecular reaction happens each time a repeating unit is produced [24]. Direct polycondensation of lactic acid results in a low molecular weight polymer because each polymerization step produces a molecule of water, which breaks down the polymer chain. It is therefore necessary to remove the water during condensation to produce high molecular weight PLA. This reaction requires a long time and high temperatures. Pang et al. [10] described the synthesis of high molecular weight PLA, by removing water from it using a molecular sieve.

Adjuvants that promote esterification include dicyclohexylcarbodiimide (DCC), carbonyl diimidazole, and bis(trichloromethyl) carbonate. However, the drawbacks of such adjuvants include the requirement for risky solvents, the inability to create copolymers with distinct functional groups, and greater costs as a result of the additional steps involved in the separation process. Many of these drawbacks are mitigated by the use of adjuvants. Nevertheless, residual metal and chain extenders - which are neither biodegradable nor bioabsorbable - are also present in polymers. Polymer weight can be increased by azeotropic condensation polymerization with a lactic acid step without the need for further chemicals or chain extenders. High molecular weight PLA can be separated for usage or additional purification following solvent removal [24].

3.3. Ring opening (ROP)

Ring-opening synthesis was first demonstrated by Carothers in 1932, but it was not until the development of lactide purification techniques in 1954 by Dupont, that high molecular weight PLA was obtained. PLA is obtained by opening the lactide ring (ROP), which is preferred because it allows greater control of the polymerization. Since a lactide molecule contains two chiral carbon atoms, it is possible to create three stereoisomers of lactides: L, D, and meso-lactide [10]. The chirality of lactic acid is an advantage in the synthesis of PLA with different stereoregularities, which influences the physicochemical properties of the material such as thermal and mechanical, but also the degradation properties [38].

The study of metal complexes catalysing the polymerization of lactide through insertion of a coordination mechanism (Fig. 4) has become extremely important due to the fact that obtaining high molecular weight PLA by cationic ROP of lactide is difficult, and also because the anionic ROP mechanism of lactide usually leads to problems in the control and distribution of molecular mass, mainly caused by secondary transesterification reactions [10].

The stereoisomers have very different properties, for example PLLA is semi-crystalline (T_g=67 °C, melting transition at 180 °C) whereas poly (rac-lactide) is amorphous (T_g at 58 °C). Low molecular weight PLA is brittle and therefore unsuitable for such applications. Polymer blending is a widely used method to improve the desired properties of the material and can be done with a variety of materials such as plasticisers, fibers, inorganic materials, natural polymers and biodegradable polyesters. For example, in PLA and PCL blends, mechanical properties can

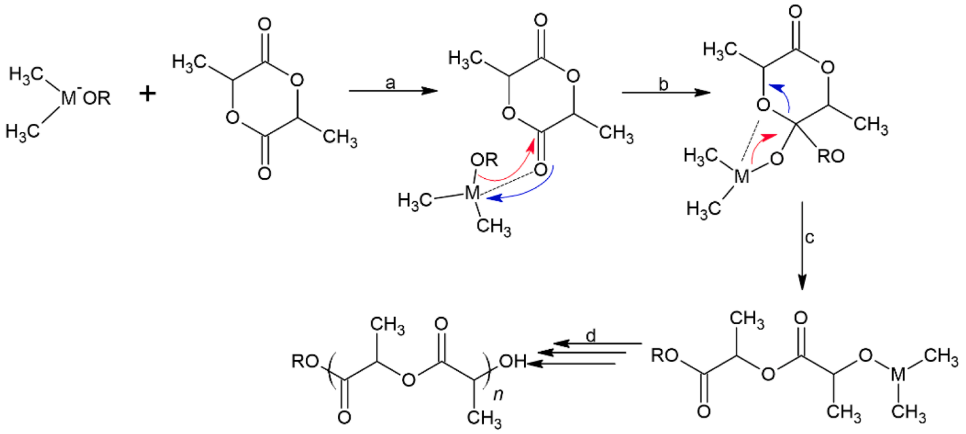

Fig. 4. Coordination-insertion mechanism in the lactide ring opening (modified from [39], with permission from RSC).

be adjusted by varying the blend composition. When the mass proportion of PLA is greater than 0.4, the modulus and tensile strength rise virtually linearly as a function of PLA composition [10].

3.4. PLA biomedical production

In the context of PLA synthesis, it is also important to discuss the advancement of its production for the biomedical area in the last 5 years. Therefore, the physical properties of the final materials are an interesting way to evaluate progress (Table 6).

4. Degradation profile of PLA

The degradation of a polymer under environmental conditions is called biodegradation and involves changes in the structural, chemical and mechanical properties of the polymer to the final stage where compounds such as water, carbon dioxide, minerals and intermediates (such as biomass and humic materials) remain. In the natural environment there are many chemical, biological and physical influences. Factors such as temperature, humidity, pH and oxygen determine the rate of biodegradation. The degree of crystallinity of the polymer will directly affect the rate of degradation as well [22].

Table 6
Comparison of the physical properties of PLA developed between 2021 and 2023.

Composition	Biomedical application/ methodology	Physical properties	Refs.
PLA + zeolite doped with copper nanoparticles	Filaments intended for additive manufacturing processes	21.48 % increase in the stiffness in the tensile test compared with pure PLA	[40]
Nanofiberd of polyurethane (PU)/ PLA	Tissue scaffords for dressing materials formed by coaxial electrospinning	The highest tensile strength reported was of 7.19 MPa, and the highest elongation was of 63.78 %.	[41]
PLA fiber	High-performance tissue repair material produced by versatile disorder-to-order technology	A mean tensile strength of 336.1 MPa and elastic modulus of 4.1 GPa was observed	[42]
PLA/Fe_2O_3 composite	3D printed biomedical and tissue engineering materials	A concentric infill pattern achieved the highest tensile strength value (50.44MPa)	[43]
PLA fiber	Braids produced by PLA yards as a tendon and ligament repair	A breaking force of 529.7 ± 34.7 N and a strain at break of 50.8 ± 3.0 % was observed	[44]
PLA	3D printed orthopaedic Equipment	The highest tensile strength reported was of 59.82 MPa	[45]
PLA	Fused deposition modeling to produce bone plates	The highest tensile strength reported was of 80.04 ± 0.70 MPa	[46]

Under industrial conditions of composting, PLA degrades due to the action of microorganisms in a humid environment producing biomass and carbon dioxide. The degradation of PLA occurs to its basic monomer, lactic acid (or 2-hydroxy-propanoic). LA is a naturally occurring organic acid because it is a metabolic by-product, its degradation occurs by non-enzymatic hydrolysis. In the body, lactic acid is eliminated by the normal cycle of cells (Fig. 5) [47,48].

Biodegradability is an important factor for both the biomedical field and the environment. The degradation of PLA involves a diverse range of mechanisms, each contributing to its breakdown. These mechanisms encompass hydrolytic, oxidative, thermal, microbial, enzymatic, chemical, and photodegradative processes. Hydrolysis plays a pivotal role in PLA degradation, as it leads to the cleavage of ester bonds, resulting in the formation of oligomers and monomers of lactic acid. Specifically, microbial strains and humidity levels are critical factors influencing the biodegradation of PLA [50].

Moreover, recent progress in PLA degradation has explored innovative strategies, such as incorporating nanoclays. This has proven effective in enhancing the degradation rate due to the presence of hydroxyl groups associated with the silicate layers. Consequently, the introduction of nanoclays emerges as a promising approach to increase the overall efficiency of PLA degradation, showcasing advancements in the field [51].

It has also been demonstrated that the chemical makeup of the backbone and terminal group, the molecular weight and its distribution, and the degrading environment all affect how PLA and its copolymers biodegrade. Because semi-crystalline PLA has a low water permeability, the rate of breakdown is comparatively modest. Due to their greater rate of water absorption than the crystalline portions, the amorphous parts of PLA undergo hydrolytic breakdown first. The development of carboxylic end groups might lead to autocatalytic degradation by catalyzing further hydrolysis. Autocatalysis is responsible for the higher rate of PLA breakdown of low molecular weight PLA or PLA containing lactides and oligomers. Due to the polymer chains' increased flexibility at higher temperatures, PLA also degrades more quickly when heated [10,52]. Elevated molecular weight PLA (e.g., 106 g.mol-1) can induce infection and inflammation because it takes two to eight years for it to fully resorb. Consequently, it is preferable to produce low molecular weight PLA (60,000 g.mol-1) since it has a quick degradation period. Moreover, polylactides' non-toxic breakdown products enhance their potential use in medicine [53]. Under environmental conditions, it degrades in about weeks or months [54].

Patients with implants may experience inflammatory responses due

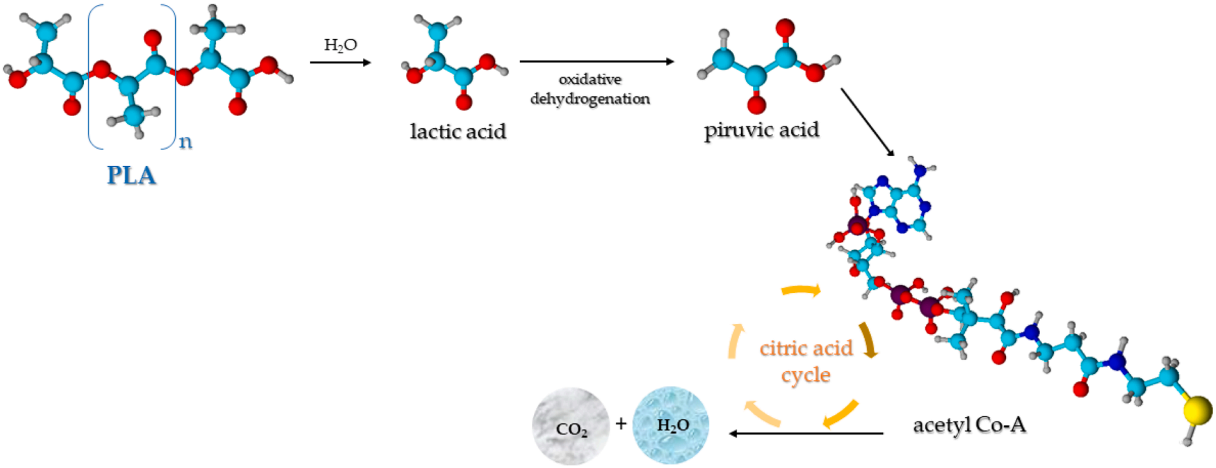

Fig. 5. Metabolic route of PLA degradation (modified after [49], with copyright permission under the Creative Commons CC-BY license).

to the prolonged degradation period of PLLA and the high crystallinity of its fragments. A mixture of D-L-lactic acid and L-lactic monomers can be utilized to overcome this problem because the latter breaks down quickly without forming crystalline fragments [48,55]. Firstly, it is necessary that the rate of degradation of the implant is compatible with the growth rate of the tissue where the piece has been placed in the body, because if the rate of degradation is faster, the tissue will not recover. However, if the pace of deterioration is too slow, the device can disrupt the tissue's functioning. Thus, it is critical to strike the ideal balance between the rate of disintegration and the rate at which the injured tissue heals while creating biodegradable prostheses. That is why the best adjustment of degradation rate versus the healing rate of damaged tissue is important in the manufacture of biodegradable prostheses, another aggravating factor is that the healing process strongly depends on the extent of the wounds and the patient [11].

PLLA degrades more quickly in alkaline media than in acidic or neutral media when evaluated in various media. It was also shown that the breakdown process was accelerated by the presence of microorganisms and enzymes. However, it has been reported that the PLLA/PDLA complex is more resistant to hydrolysis than PLLA and PDLA alone [28].

5. Biomedical applications of PLA

TEvery year, new therapeutic procedures emerge, and tissue engineering is advancing exponentially. Implants, synthetic materials and prostheses made from polymeric materials aim to replace whole or partial organs and tissues with lost functions. Polymeric materials have gained prominence in the medical field in recent decades due to their applicability in tissue replacement and support, as well as in the controlled release of drugs. Polymeric materials are classified according to their behaviour in living tissues as biostable, bioabsorbable (biodegradable or bioresorbable) and partially bioabsorbable [52]. Often the implants need to remain in the patient temporarily, so bioabsorbable polymers are more appropriate. Biocompatibility is very important because prostheses and implants are foreign bodies, so there is always the possibility that the immune system will have a chronic rejection of the implant, which can lead to the destruction of the implanted area [56, 57].

As life expectancy increases, so does the need for solutions to a wide range of medical problems. Tissue engineering is a multidisciplinary science involving both engineering and biology, with the aim of reconstructing living organs and tissues [58]. In this sense, the main area of activity in tissue engineering is scaffolds, which are supports or 3D matrices in which cells, usually taken from the patient, are deposited for later implantation. The materials used for scaffolds require very specific properties, but mainly they must be biocompatible, antiseptic, non-toxic, non-mutagenic, non-teratogenic, non-antigenic, non-carcinogenic, and not cause morbidity [59].

Tissue engineering aims to maintain, repair, or enhance tissue function by combining scaffolds, chemicals, or bioactive cells. Though the three elements are not always necessary, a biocompatible scaffold is necessary to provide the essential architectural signals for the regeneration of large lesions. PLA-based products can be divided into two groups: those consumed directly by the patient as dressings and drug delivery devices, and those used surgically as support for skin regeneration, implants and sutures [38].

PLA, as a biocompatible polymer, has been used for medical applications in implants and medical devices since the 1960s, the polymer degrades over time, i.e. there is no need for the implant to be removed. The end product of PLA degradation, lactic acid, is produced naturally by the human body and is therefore non-toxic, which is one of the main reasons why this polymer is used in medical applications. These implants include tissue growth, bone grafting, and devices for fixation in cases of fractures [3]. Some PLA properties that enable its application in the medical area are presented in Fig. 6.

In order to enhance its mechanical properties and expand its applicability for tendon and ligament repair, fracture stabilization, and other uses, PLA is commonly mixed with other polymers and/or proteins, such as collagen, carbon fiber, polyglycolic acid (PGA), and hydroxyapatite

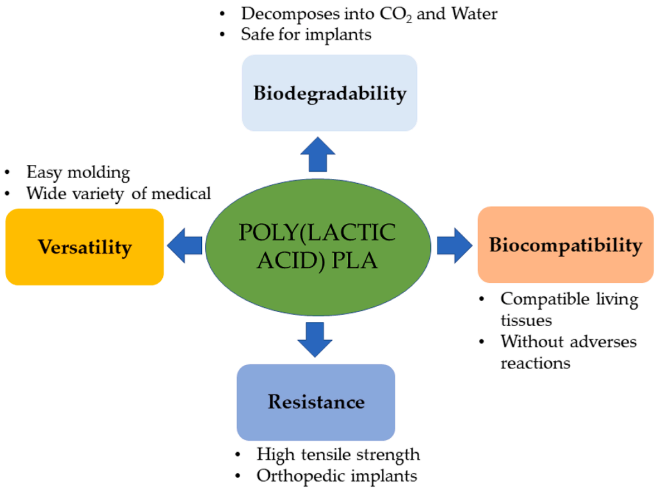

Fig. 6. PLA properties that are interesting for medical application (modified after [60]).

(HA) glass fiber. According to reports, lactic acid build-up from PLA decomposition lowers the pH of cells and tissues, causing inflammation of the tissue that comes into contact with the implant. A PLA-chitosan composite could alleviate this problem because chitosan neutralises the pH [61]. Additionally, by promoting the formation of natural cells surrounding the polymer portion, PLA composite implants can aid in the treatment of any organ loss or dysfunction. PLA dermal fillers are approved by the American Society of Plastic Surgeons for use in facial enhancement. These fillers function by inducing the formation of collagen in the human body [3].

Currently, PLA is the most widely used biocompatible polymer in the medical field, because it does not cause carcinogenic or toxic effects (Fig. 7).

Furthermore, lactic acid is removed and incorporated into the tricarboxylic acid cycle following PLA breakdown. Some PLA-based materials can only be utilized in certain limited ways because of their hydrophobicity and lack of functional groups, even though PLA and its copolymers are biocompatible enough for a range of biomedical purposes. Research is being done on PLA surface modification as a direct means of producing PLA-based materials with higher biocompatibility. To control the interface between PLA materials and cells, extracellular proteins, such as collagen, vitronectin, fibronectin, entacin, and RGD peptides, have been covalently or non-covalently bound to the PLA surface [10].

Despite much information, there are few papers discussing the real clinical applications of these implants. This could be because there may be issues with the PLA implants' compatibility with the human body. PLA implants can break down quickly or slowly, which may trigger a human host's defense mechanism. The effect of toxicity may appear with long-term use. For more than ten years, the application of PLA in medicine has been studied including for the replacement of metallic devices. This polymer has the advantage over metals as it is not corrodible and also does not cause distortion in molecular resonance images. In 2010, researchers at the Fraunhofer Institute in Germany developed screws made with PLA composites. The authors stated that these screws are an excellent substitute for titanium surgical implants since they precisely replicate the strength of actual bone. PLA medical products have been offered by companies like Arthrex TM, Phusis,

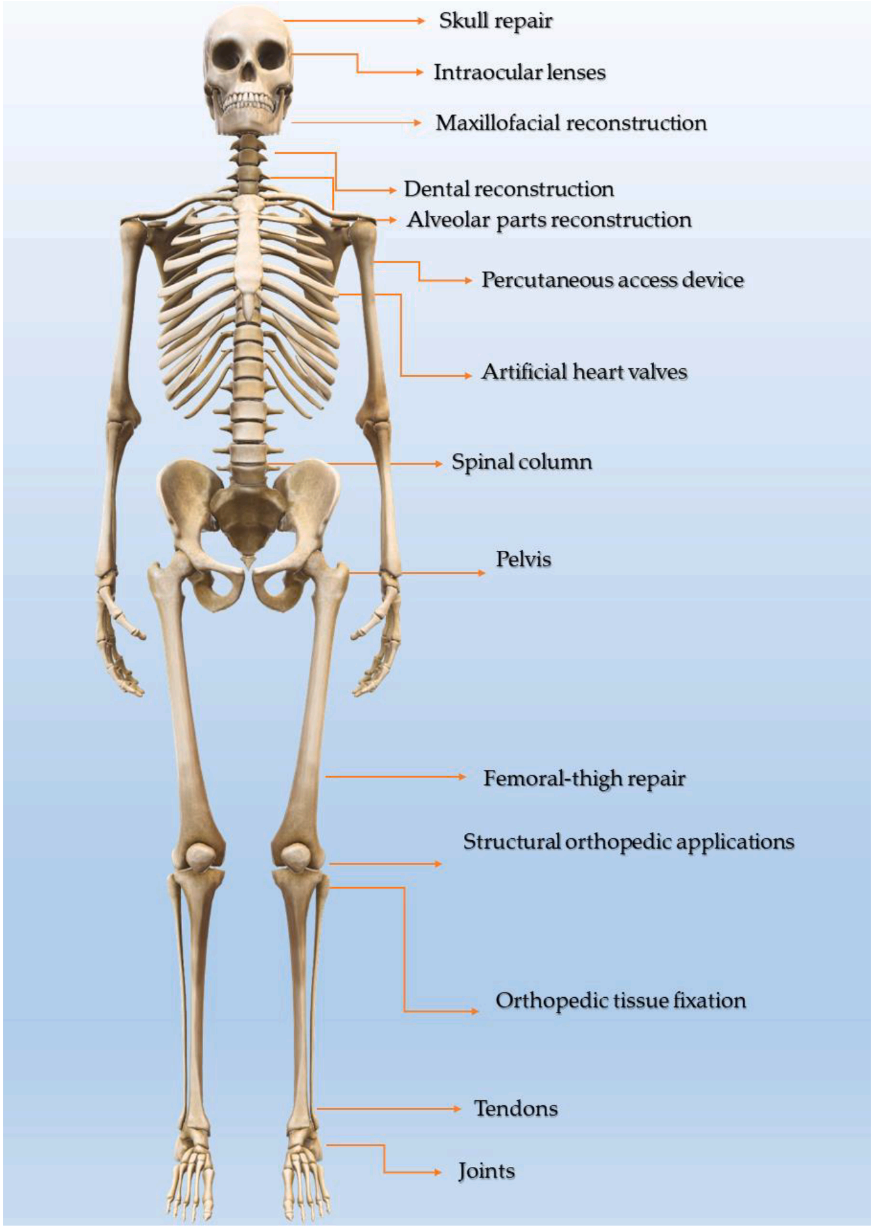

Fig. 7. Applications of PLA in the medical field [62–76].

Gunze, Takiron, and Linvatec for usage as suture anchors, bars, micro plates (bone fixation), and screws [3].

Most of the medical devices mentioned are made through a process of stretching PLLA with Mw > 7.0.104 Da. Stretching, which is made feasible by the PLA's orientation and crystallinity, is a process that strengthens the devices' characteristics to resemble real bones. The piezoelectric property of the devices, which is linked to bone development, seems to be impacted by the stretching process of PLLA. Although PLA appears to be a superior material than metal, its effect on bone resorption is slower in the context of bone grafting. There are still some unclear mechanisms underlying the breakdown of PLA in the human body [3].

When it comes to applications where extended force retention is necessary, including ligament and tendon restoration and stents for vascular and urological surgeries, PLLA fibers are the ideal option. Another important application for PLLA is injectable microspheres that can be used in reconstructive facial surgeries where this filling is placed temporarily [77].

5.1. *Tissue engineering (Scaffolds)*

A living tissue is defined as a scaffold, synthetic, natural or a combination of both, on which living cells, whether applied before implantation or not, will proliferate [78,79]**.** The scaffold not only offers mechanical stability but also serves as a model of three-dimensional organization and support for the cells [78]. The success of the implant is largely dependent on the scaffold-cell interaction, the pace of polymer degradation, the rate of cell biosynthesis, and the cellular inoculation of the polymer. Based on the type, location, and severity of the lesion, a different scaffold should be employed [80]. The term "biocompatibility" was redefined by Williams in 1987 as the ability of a material to function in a specific application with an appropriate tissue response [81]. Some requirements for a biomaterial to be suitable for tissue engineering applications are presented in Table 7.

The selected scaffold must be biocompatible. It must elicit a favourable cellular response and, at the same time, provide an adequate immune response to the host of the tissue or implant. Another criterion, more difficult to achieve, is to obtain a match between the rate of degradation of the scaffold and the growth of the new tissue [78,83]. A scaffold is never totally solid or rigid. To ensure that there is enough room for waste materials and nutrients to enter and leave, the pores should be at least several times larger than the size of the cells that will be seeded.

It has been demonstrated that PLA nanofibrous scaffolds are a flexible instrument for tissue engineering, serving as a substrate for biofunctionalization or a three-dimensional topographic surface for cell fixation. In addition to scaffolding, PLA nanofibers have also been used for drug release, especially when prepared by electrospinning. Direct adsorption of the drug onto the nanofibers' surface, which takes advantage of the inherent surface area of materials at the nanoscale, is the most straightforward technique for drug loading [38].

Nanofibers have the advantage of easy evaporation, excellent oxygen permeability and can also be manufactured to inhibit contamination by microorganisms due to their ultra-thin pores [83]. Scaffolds made of PLLA nanofibers resemble fibrillar collagen in structure, but they also have macropores that allow for cell movement and nutrition exchange [38].

Table 7
Biomaterials' properties required for tissue engineering (modified after [82]).

Properties	Features
Atoxic	Non-mutagenic, non-allergic, nonpyrogenicity, nonhemolyticity, ononcogenicity etc.
Effective	Performance, functionality, durability, etc.
Sterile	Autoclave, dry heating, irradiation ethylene oxide gas, etc.
Biocompatibility	Interfacial, mechanical, biological

The blending of PLA with other materials is common and aims to improve the properties of the final product. Thus, nanodiamond (ND) is an accessible and chemically stable agent that, when present on the surface of biomaterials, acts as a cell growth support. Then, the stability and biocompatibility of the final product increases when ND is incorporated into polymeric materials [84].

Electrospun PLA/ND fibers with a low ND loading (0.1-1 wt%) were evaluated. PLA and ND were combined with the aim of improving the biological properties of the final product. The results showed that all PLA/ND scaffolds significantly improved in bioactivity and cell adhesion. Bioactive PLA/ND fibers have the ability to attract and bind cells to a damaged area that they cover or bind to. Certain materials with higher hydrophilicity are particularly desired in the medical field. All of the ND-containing scaffolds were found to be more hydrophilic than PLA alone [84].

To promote drug-scaffold binding, direct adsorption depends on non-covalent chemical interactions between the drug and the polymer, such as electrostatic and Van der Waals interactions. Drugs are more able to diffuse from the polymer surface of nanofibers because of their high porosity and surface area. This often results in a significant initial release of the drug when in contact with the medium, a process known as burst release. This method works especially well with medications that may be sensitive to the voltage used in electrospinning or to organic solvents [38].

PLLA tablets produced from raw PLLA pressed were used as scaffolds for cranial repair of injured mice; the animals were monitored for 6–9 months and no infection was observed during this time, while a fibrous scar was formed above the PLLA scaffold and osteoblasts, osteocytes, and osteoclasts proliferated around the scar, indicating the osteoregenerative potential of this PLLA scaffold (Fig. 8) [85].

5.2. *Drug delivery*

The controlled administration of drugs has many advantages such as the reduction of premature degradation, improvement in absorption, greater support in the concentration of the drug within the therapeutic window and reduction of side effects. Nanotechnology has made it feasible to influence drug release, primarily in the areas of vaccination and anticancer therapy. The large volume to surface area ratio, the ability to target and react to stimuli, the biodegradability, biocompatibility, and low cytotoxicity of nanoparticles are among their benefits. This makes nanoparticles especially safe and effective for both the loading and the delivery of drugs to diseased cells at an ad hoc regulated rate, thereby bringing anticancer therapy closer to the ideal of personalized medicine. These nanoparticles enable the encapsulation of hydrophobic compounds in addition to shielding the antigen charge [9].

The use of poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA) matrices is primarily based on their biodegradable profile, but also these polyesters can have their mechanical and physicochemical properties tailored to biosafety by selecting the appropriate copolymerization and functionalization [79]. These polymers are approved by the FDA for human use in medical devices and delivery systems (e.g., bone implants, sutures, screws, and as antigens in vaccines) [9].

A glioblastoma has been treated with a polymeric drug delivery system (nano-implant) consisted of PLGA-PLA-PCL blend loaded with temozolomide (TMZ - 20 % wt), an anticancer drug (Fig. 9) [86]. This work presented a great survival rate for animals treated with long term TMZ release, whereas the ones treated with a faster TMZ release had a tumor recurrence superior than 50 % of the population.

5.3. *Orthopaedic use (cartilage and meniscus)*

Cartilage is a tissue that supports the body and transfers the applied load. One of the most common types is fibrocartilage, found in the meniscus and also in the fibrous ring of the intervertebral discs of the

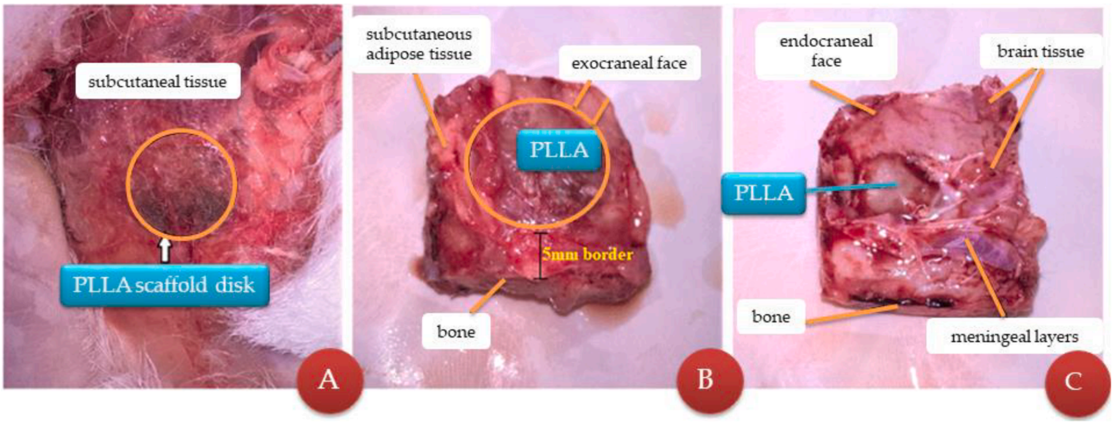

Fig. 8. Cranial defects healed with PLLA scaffolds: (a) cranial defect with fibrous scar, (b) exocranial view, and (c) endocranial view (adapted from [85], with copyright permission under the Creative Commons CC-BY 4.0 license).

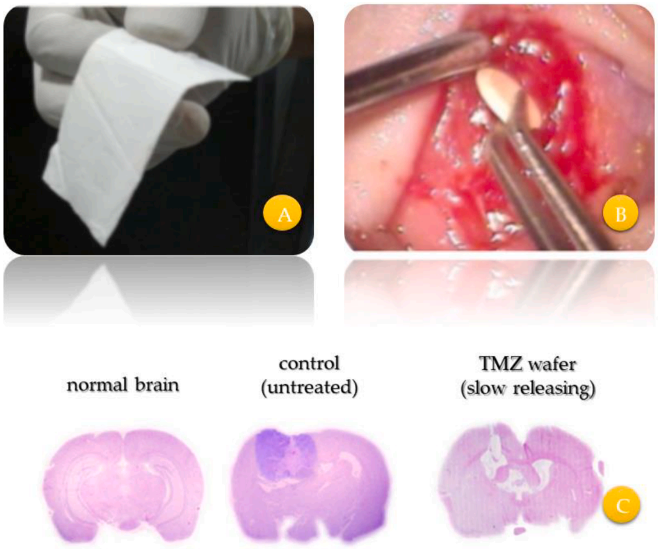

Fig. 9. PLGA-PLA-PCL electrospun nanofibers used as brain-implant for controlled TMZ release to treat recurrent glioma: (a) PLGA nanofibers, (b) photograph of the surgery to introduce the nano-brain-implant, and (c) brain sections of different rat groups studied (adapted from [86], with copyright permission under the Creative Commons CC-BY 4.0 license).

spine. The meniscus is semicircular structure located in the central region of the knee, with two menisci by leg. They improve the fit between the femur and tibia and are essential for maintaining the normal biomechanics of the knee joint. Fibrocartilage is an extracellular matrix composed mainly of collagen, water, and type I cells [58,87,88].

Due to the articular cartilage and the complexity of the region, lesions of meniscus have little healing capacity, especially in the internal avascularised part, but also because this type of lesion occurs more frequently in patients of advanced age. Osteoarthritic alterations result from the loss of articular cartilage, requiring meniscus repair. The current standard surgical procedures recommendedfor this kind of injury are meniscal repair and partial meniscectomy. Tissue engineering has gained a lot of space due to the shortage of donors in cases of meniscus replacement with a donor graft or with a synthetic scaffold. Researchers have demonstrated that synthetic scaffolds can be used to regenerate tissue. In a study, the authors synthesized human meniscus-like cartilaginous tissue using a 3D printed PLA-PCL scaffold that was loaded with growth hormones [58].

Several other studies have been conducted aiming at meniscus repair. Bioabsorbable polymers have been used to replace damaged menisci. PLA is an excellent meniscus substitute in humans due to its half-life of six months for moisture resistance and its tensile strength of 50 MPa with a modulus of 3.4 GPa. A molded, bioabsorbable polylactic acid construct. used in meniscus repair, showed a 95 % clinical success rate with minimal side effects and ideal recovery. According to a comparative analysis of six meniscus repair methods, these PLA implants exhibited a markedly decreased failure and stiffness rate in comparison to two other repair methods [9].

Veth et al. (1986) [89] published one of the earliest experiments using biomaterials as a substitute for cartilage repair, studying in a canine model a polyurethane-PLLA (PU-PLLA) graft reinforced with carbon fiber. PLA-based biomaterials for meniscus and cartilage regeneration are becoming more popular, despite the fact that this substance encouraged the growth of fibrous tissue and the sporadic production of hyaline cartilage. For cartilage injuries, a single-step, less invasive method that produces textiles that closely resemble the original tissue's composition, and requires less time to heal, would be more practical. Tissue engineering has faced significant challenges because to the intricate nature of hyaline cartilage tissue. Consequently, a variety of commercially accessible goods, including scaffold-based products, have been produced as a result of studies that focused on replicating the intricate arrangement of zones, cell kinds, and cell orientation in the body. There are currently two systems based on PLA scaffolds that are being used clinically for cartilage repair: *BioSeed-C®* and *TRUFIT CB™*. The disc *BioSeed-C® 3-D* of *Biotissue Technologies* (Fig. 10) uses a scaffold based on PGA/PLA and polydioxanone (PDO). For this treatment, the patient must receive intervention twice, the first for cell culture and the second for tissue implantation. The scaffold is not appropriate for patients who are sensitive to heparin, while patients with deep bone lesions must have a previous spongioplasty. A significant drawback is the possibility of infectious illnesses and the product's vulnerability to denaturation when exposed to alcohol [87].

Smith and Nephew*'s TRUFIT CB™* plug is composed of a bi-layer of polyhydrate (D-L-lactide-coglycolide) (PDLGA) and calcium sulfate. The PDLGA layer promotes cartilage production, while the calcium sulfate layer promotes bone formation. This technique is utilized to repair osteochondral lesions in the knee cartilage. This process, in contrast to the previous one, can be completed in a single visit; nonetheless, results have only marginally improved, and additional clinical trials are required to fully understand the effectiveness of this system. It is well known that adding PLGA to collagen improves its mechanical properties and cell adhesion, and that adding BMSCs at the same time promotes tissue integration and, ultimately, osteochondral regeneration. No PLA meniscus repair products are available on the market yet [87].

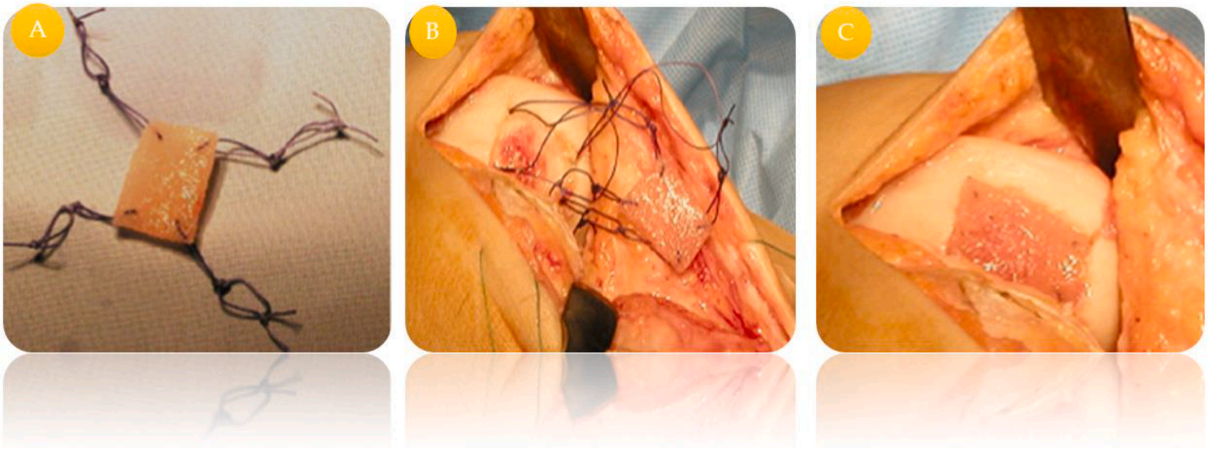

Fig. 10. BioSeed-C® arthrotomic implementation: (a) BioSeed-C® with bioreasorbable threads, (b) BioSeed-C® pulled through femoral bone with threads help, and (c) fixing the graft (epud reprinted from [87], with permission from Elsevier).

5.4. Cardiac use

The reconstruction of the chest wall with synthetic sticks, which has the function of stabilizing the box, is a procedure with several limitations. Many patients suffer from inflammation in the implanted area; the incorporation of the implant into the tissue is incomplete which causes infections, erosion in underlying viscera and a second surgery is required to remove the implant. Properties such as a certain degree of malleability and rigidity, as well as inertia and radiodensity, are necessary to ensure the prostheses stabilization [90]. Depending on the location of the defect, there may be a greater need for a material that withstand stress in all directions. Synthetic meshes can be made of polypropylene, polytetrafluoroethylene, polyglactin and methyl polypropylene methacrylate composite mesh [91]. Osteochondral defects can be repaired using this method. One study found that patients receiving bovine pericardial fragments and PLA bars—alone or in combination—for chest wall stabilization came to the conclusion that the fragment plus PLA bars is recommended for diseased areas because of the systemic antibiotics that were administered afterward. It also showed that there is no need for a second surgical treatment to remove the product [9].

Additionally, PLA can be used to treat small- to moderate-sized exterior abnormalities, as well as lateral chest wall deformities. If there is enough soft tissue behind the defect in a single or double ribs , PLA bars alone are the most appropriate option for primary repairs and redo pectus. Overall, this type of procedure with biomaterials was a promising option and with good results in the evaluated patients [9].

In addition to rib cage reconstruction, biopolymers can be applied as resorbable stents for coronary angioplasty procedures. In this case, the implant has the function of providing mechanical support, reducing vein occlusion, reducing the risk of late thrombosis to the damaged artery and improving the image of the lesion [92].

Bioabsorbable coronary scaffolds have been developed by numerous companies; one important advantage of coronary scaffolds is that the material is broken down by the human body, so that removal of the component does not require surgery. Since the initial generation of drug-eluting stents has been linked to many rates of late thrombosis, late cure, chronic inflammation, and hypersensitivity, the development of bioabsorbable or biodegradable stents for coronary artery disorders is crucial. Resorbable polymer stents are designed for application in living tissues, avoiding these side effects; in addition, these devices remain flexible even after the onset of degradation without the need for mechanical removal.

In the United States, the first drug-eluting stent was produced with a bioabsorbable polymeric coating, The Synergy drug-eluting stent (Boston Scientific, USA), which is made of an alloy of platinum and chromium, has an ultra-thin PLGA coat combined with everolimus to create an abluminal coating. The metal piece remains in the vein after the drug is discharged, which lowers the risk of late thrombosis, for several months after the lining dissolves. In a study conducted in pigs, endothelialization took 28 days and polymer reabsorption took 4 months to complete [93].

Another possible use of PLA, is in ureteral stents. Li et al. [94] evaluated the use of PLA stents in the treatment of lesions in the urethra, showing that PLA stents cound be degraded [94].

Keiji Igaki and Hideo Tamai created the first bioabsorbable cardiac stent made of high-molecular-weight PLLA monofilament, having a zigzag helical coil structureto be implanted in human coronary arteries [95]. Clinical trials suggested the long-term safety of Igaki-Tamai stent (Kyoto Medical Planning Co, Ltd, Kyoto, Japan), which mostly disappeared within 3-years time. Compared to sirolimus-eluting stent, the mechanisms of vessel healing in a chronic phase were found not to be the same, but open new perspectives regarding the use of bioabsorbable drug-eluting PLLA stent for a long-term safety use [95].

5.5. Suture/dentistry

Polylactic acid and copolymers have also been tested in several wound-related applications, such as surgical sutures, tooth extraction wound healing, and prevention of postoperative adhesions [96].

In the study by Qin et al. [97], PLA films were synthesized based on polymer mixtures to avoid postoperative adhesions. The PLA was mixed with polytrimethylene carbonate (PTMC) and the films were compared with those of pure PLA. The results showed that the mixtures were more flexible than pure PLA, so it is concluded that the mixture is more suitable for wound coverage; in addition, the authors also reported that PLA/PTMC and PLA films were not cytotoxic. Furthermore, pure PLA had higher tensile strength, Young's modulus, and glass transition temperature than the mixture. When testing PLA to enhance the healing of tooth extraction wounds, Brekke et al. [98] showed that the incidence of mandibular third molar extraction wound failure was significantly decreased with PLA surgical dressings during the entire study period [98,99].

The USFDA approved Atridox®, a medication made by Atrix Laboratories in Colorado, USA, in 1998 to treat periodontal diseases. This product contains a bioabsorbable gel that is mixed with N-methyl-2-pyrrolidone (NMP) and PLA. This disease causes infection in the region around the teeth. The may start with gum inflammation and develop to a more severe degree affecting the bone and soft tissue that support the teeth. The treatment consists of the action of the polymeric gel that fills and then solidifies to a wax consistency when it comes into contact with the gingival crevicular fluid. The gel reduced the anaerobic pathogen count to 60 % within 6 months of treatment, and led to a sustained release of doxycycline over a period of 7 days. Atrisorb®, a synthetic absorbable barrier with doxycycline for directed tissue development in periodontitis patients, is another PLA-based product that can be used [90–92].

A local anesthetic-eluting suture from electrospunned PLGAnanofibers, and embedded with bupivacaine, showed a local analgesia up to one week after surgery and healed normally without any other interventions [100] (Fig. 11).

6. Recent advances and future prospects

Regarding the application of PLA in the medical field, innovative research is introducing promising technology, such as electrospinning, to foster the potential of this biomaterial for a wide range of applications (Table 8).

The composition of such materials shows that blends with other biopolymers, synthetic/plant fibers and therapeutic compounds ensure that the final product has the strength, biocompatibility and applicability needed in sutures, scaffolds, and prosthesis. Also, advances in the methodology of production are important to the future of PLA. Electrospinning, coating processes, 3D printing are highlighted as current technologies associated in this manufacturing. Therefore, further studies in both composition and methodology are essential for the dissemination of PLA in the market – to obtain a product that is safe, comfortable, cost-effective, and environmentally viable, as an alternative carbon source [5].

Also, the current trends can be analysed by quantitative bibliographic research to contextualize the subject at an international level and assess their relevance. On December 18th, 2023, a search on the Scopus database using the keywords ‘poly lactic acid’ returned 18,341 results. By adding the keyword ‘medical’ to the search, 1002 articles were found published between 1969 and 2023. A bibliographic analysis was done in the form of a bibliometric map of terms, to facilitate the visualization of the topics associated with PLA medical applications. The retrieved results were exported to the Vosviewer software (version 1.6.18, [119,120]) to analyse the documents and generate a map of terms (Fig. 12). Among the most recurrent keywords, the following topics stand out: poly lactic acid, lactic acid, biocompatibility, medical

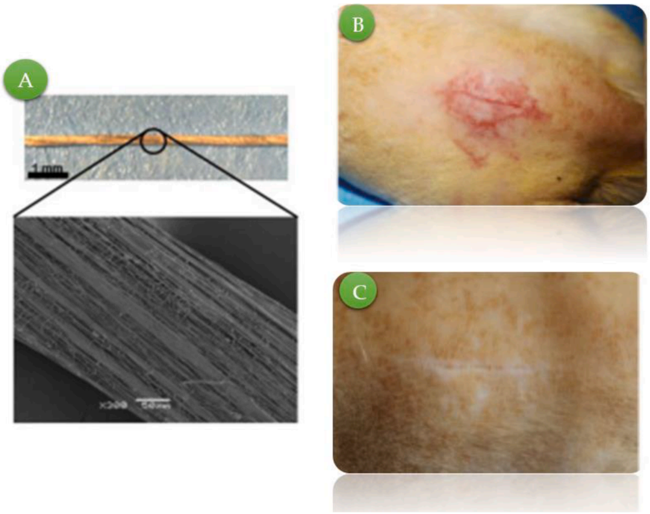

Fig. 11. PLGA suture: (a) SEM micrograph of PLGA electrospunned, (b) rat’s left dorsal flank right after closure with PLGA suture drug-eluted (bupivacaine), and (c) the same mentioned incision after 2 weeks (adapted from [100], with copyright permission under the Creative Commons CC-BY license).

Table 8
Recent studies of PLA for medical applications (years 2020–2023).

Application	Composition	Production	Results	Ref.
Suture materials	Chitosan/ polyvinyl alcohol (CHS/PVA) (30:70) and PLA	Dual electrospinning with aligned collection	Nanofibers yarns presented morphology and antibacterial activity suitable to surgical application.	[101]
	PLA impregnated with naproxen and ibuprofen	Fibers were developed by extrusion or electrospinning and impregnation using supercritical CO_2	Electrospun PLA films had a better response as an anti-inflammatory suture.	[102]
	Low-density polyethylene (LDPE)/ PLA/ CHS	Monofilament produced by extrusion using different blend compositions	The material developed have strength, antimicrobial capacity, and biodegradation suitable to tendon sutures.	[103]
	PLA sutures coated by a polyglycolide/ polycaprolactone (PGA/PCL) blend carrying ciprofloxacin drug	PLA sutures were acquired commercially, and the carrier and drug were impregnated by a dip-padding process	The initial suture presented a stitching resistance. However, increasing the PCL granted more stability. The coating dissolution also affected positively the drug release.	[104]
	Agave sisalana leaf fibers coated with strontium oxide (SrO) and PLA as a carrier of ciprofloxacin	Plant fibers were treated by a mercerization and bleaching processes proceeded by a dip-coating	The plant fibers offered an adequate strength, antimicrobial properties, and radiopacity retention for a period superior to 28 days.	[105]
	PLA/Gelatin blend (9:1)	Mats were produced by electrospinning	Gelatin conferred an 30 % boost in the material biodegradation compared to a pure PLA suture.	[106]
	PLA-PCL	Bilayer nerve conduits were electrospun with outer PLA-PCL	Material had great potential to nerve regeneration due to its biomechanical properties.	[107]
Scaffolds	PLA/PCL composite	Three ten-layered box scaffolds were produced by melt electrowriting	The blend improved the strength and cell interactions compared with the pure PLA and PCL scaffolds. The biocompatibility was essential to be applied in heart tissue engineering.	[108]

(continued on next page)

Table 8 (*continued*)

Application	Composition	Production	Results	Ref.
	PLA	Scaffolds were 3D printed using optimal manufactured parameters	The scaffold porosity was analysed to ensure biomechanical compatibility in a trabecular bone replacement.	[109]
	Graphene/PLA	Blend were 3D printed using a micropattern	The morphology and the presence of graphene guarantee the cells alignment and differentiation, essential to tissue engineering.	[110]
	PLA/CHS composite	Scaffolds were 3D printed by fused filament fabrication	The optimal response to mechanical properties were with 1 wt% chitosan, 100 % of infill density, and 70°C annealing temperature	[111]
	PLA scaffold coated with hyaluronic acid/PVA	The scaffold was 3D printed and the coating was done by electrospinning	The material presented an adequate response in biomechanical properties, such as porosity, to be applied in cartilage regeneration	[112]
	Collagen/PLA	Scaffolds were produced using textile weaving technique	The blend used ensured mechanical properties and cell growth adequate to treatments to repair tendons	[113]
Prosthesis	PLA/Carbon Fiber	A pylon prosthesis was 3D printed with a polygonal diameter	The material studied is cheaper and lighter than commercially available pylons. It also performed well in the strength tests, being able to support the patient's weight.	[114]
	PLA/Carbon Fiber + epoxy resin	A hip femoral stem was developed using layers of plate PLA manufactured by a fused deposition	The characterization techniques permitted to conclude that the prosthesis have the mechanical properties similar to the hip and the cell viability is adequate to its use.	[115]
	PLA	A foot prosthesis was 3D printed by fused deposition	An optimized weight was obtained by topography studies and simulated strength tests proved its applicability.	[116]
	PLA/Carbon Fiber	An above knee socket was manufactured by 3D printing	Strength tests determined that the carbon fiber was necessary in the manufacturing to achieve satisfactory results (sustain up to 5 times the patient's weight)	[117]
	PLA	Neovaginal prostheses were 3D printed (PACIENA®)	Compared to the Skin Graft procedure, the prothesis granted reduced surgery and hospitalization times with similar cell viability.	[118]

applications, tissue engineering, scaffolds, biomedical applications, and cosmetic techniques, among others. This demonstrates the great potential of using PLA polymer in different areas such as health, medicine and pharmacy. Also, the techniques (electrospinning, 3D printers, fused deposition modelling) and important material's characteristics (crystallinity, antibacterial properties, cell viability) further consolidate the PLA advancements in the biomedical field.

7. Conclusions

Polylactic acid (PLA) has emerged as a versatile and promising biodegradable polymer with widespread applications. Its properties, including physical, thermal, and mechanical aspects, are influenced by factors like molecular distribution, stereochemistry, and composition. Control over polymerization allows tailoring PLA to be amorphous or semicrystalline. Blending it with stereo complexes enhances mechanical and thermal resistance, broadening applications. Incorporating natural/synthetic fibers and nanofillers leads to composites with improved strength and stability. Copolymerization enables a spectrum from flexible to rigid, high-strength polymers. Its biodegradability and biocompatibility make PLA a valuable polymer in biomedical field, with potential for use in tissue engineering and in drug delivery. Challenges like degradation rates persist, but ongoing research aims to overcome them. Future PLA research promises tailored materials with advanced properties. Exploitation of copolymerization and reinforcement strategies is ongoing. PLA's renewable origin and biodegradability position it favorably for eco-friendly alternatives. Ongoing research regarding degradation mechanisms and inflammation mitigation will also expand PLA's biomedical applications. In conclusion, PLA's molecular properties, synthesis methods, and applications offer a vast landscape for innovation, which will significantly impact diverse industries and contribute to the evolution of biodegradable materials.

Ethics issues

This work does not raise any specific ethics issues.

Data availability statement

This work does not contain authors own data.

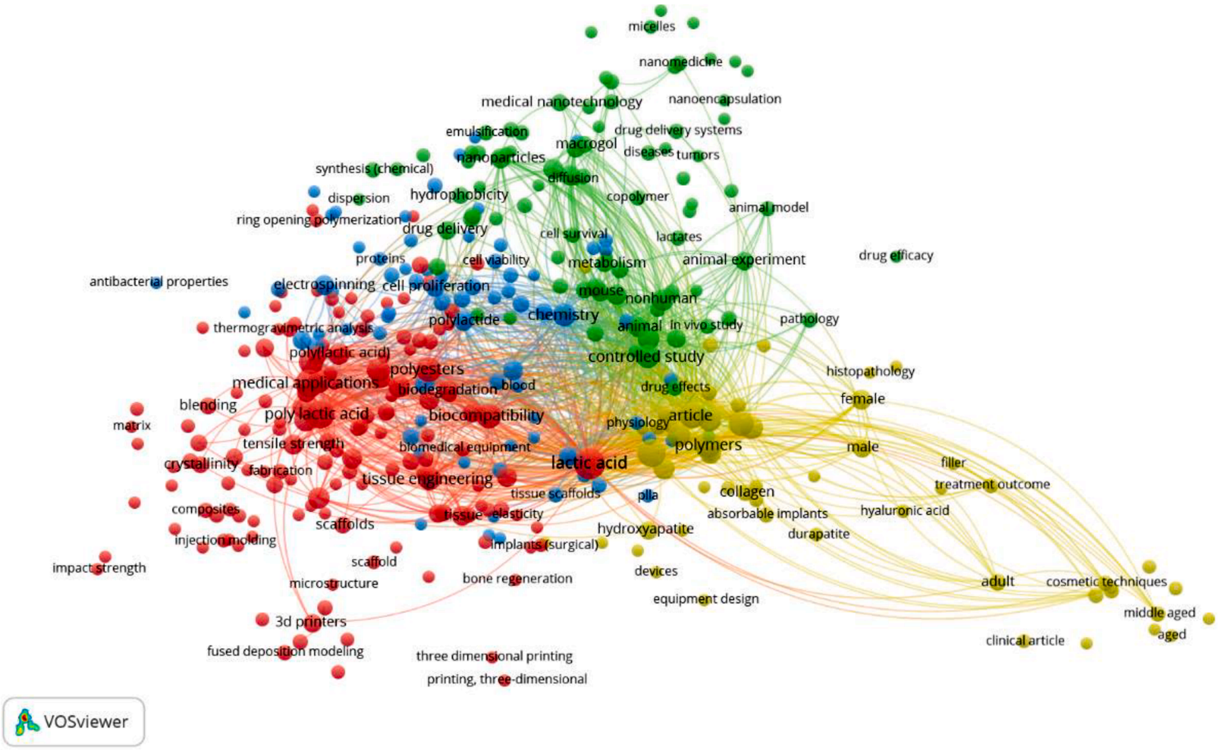

Fig. 12. Map of search terms for poly lactic acid. The data was extracted from the Scopus database and processed by the VOSviewer software on 18th December 2023.

CRediT authorship contribution statement

Nadia G. Khouri: Conceptualization. **Juliana O. Bahú:** Data curation. **Cristina Blanco-Llamero:** Formal analysis. **Patricia Severino:** Investigation. **Viktor O.C. Concha:** Methodology. **Eliana B. Souto:** Supervision.

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.

Data availability

No data was used for the research described in the article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2024.138243.

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