



Production methods and applications of bioactive polylactic acid: a review

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Abstract

Bioplastics appear as an alternative to fossil fuel-derived plastics because bioplastics are carbon neutral and often biodegradable, thus potentially solving the issues of plastic pollution and climate change. In particular, polylactic acid is a substitute for traditional petrochemical-based polymers. Here, we review polylactic acid production with focus on surface modification and integration of bioactive compounds. Surface can be modified by chemical treatment, photografting, surface entrapment, plasma treatment, and coating. Bioactive compounds can be incorporated by encapsulation, impregnation, melt blending, solvent casting, electrospinning, and in situ polymerization. Biomedical and packaging applications are discussed.

Keywords Polylactic acid · Bioactive compound · Modification of polylactic acid · Food packaging · Biomedical application · Bioeconomy

Introduction

In response to global pollution caused by nondegradable plastics, the emergence of biodegradable materials stands as a promising solution. Diverging from conventional plastics with enduring environmental consequences, the key advantage of biodegradable plastics lies in their inherent ability to decompose under environmental conditions and with the assistance of specific microorganisms. A notable example is polylactic acid that has gained significant attention for its potential to address waste disposal issues and reduce dependence on petrochemical plastics. Polylactic acid's unique combination of properties makes it suitable for a wide variety of applications. Its transparency, tensile strength, wearability, solubility profile, biodegradability, breathability, and barrier properties make it an attractive choice for food and beverage packaging, while its biocompatibility and non-toxicity are highly valued in biomedical applications (Hong et al. 2021; Yusoff et al. 2021; de Albuquerque et al. 2021).

The conventional method for lactic acid production, the precursor of polylactic acid, relies on two primary approaches: (1) utilizing raw materials from agro-dedicated crops and (2) employing the petrochemical route. However, these conventional methods pose challenges, involving competition for resources with feed and food production and presenting economic and environmental difficulties. In contrast, a novel and contrasting paradigm for sustainable polylactic acid production explores fermentative processes, emphasizing the use of new and sustainable sources of sugar and starch. Nevertheless, this alternative address has challenges in land-use competition, in the purification of lactic acid, and in microbial fermentation efficiency, the last limited by, among others, the microorganisms' conversion of pentoses to lactic acid via fermentation. The ongoing pursuit of these sustainable pathways not only enhances the eco-friendly profile of polylactic acid but also positions it as a promising candidate for a more sustainable future in the realm of biodegradable and renewable materials (Cubas-Cano et al. 2018; Baran and Erbil 2019).

Polylactic acid's family includes poly(L-lactide), poly(D-lactide), poly(DL-lactide), poly(meso-lactide), and copolymers made from monomers. The polymerization of L-lactide results in poly(L-lactide), while poly(D-lactide) is formed through the polymerization of D-lactide. The stereochemistry of the polymer structure determines whether polylactic acid exists in either a semicrystalline or amorphous

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state. Poly(L-lactide) and poly(D-lactide) are examples of semicrystalline polymers, exhibiting a structured molecular arrangement, while poly(DL-lactide) and poly(meso-lactide) are amorphous polymers (Horváth et al. 2022; Ali et al. 2023).

In general, there are two main methods of polymerization to achieve polylactic acid with high molecular weight: (i) the application of standard polycondensation, where polylactic acid with low molar weights can be synthesized, which includes direct polycondensation, azeotropic dehydration polycondensation, and solid-state polymerization, and (ii) the ring opening polymerization (Ramezani Dana and Ebrahimi 2023). A resume of the main synthesis methods of polymerization used in the production of polylactic acid is described in Fig. 1.

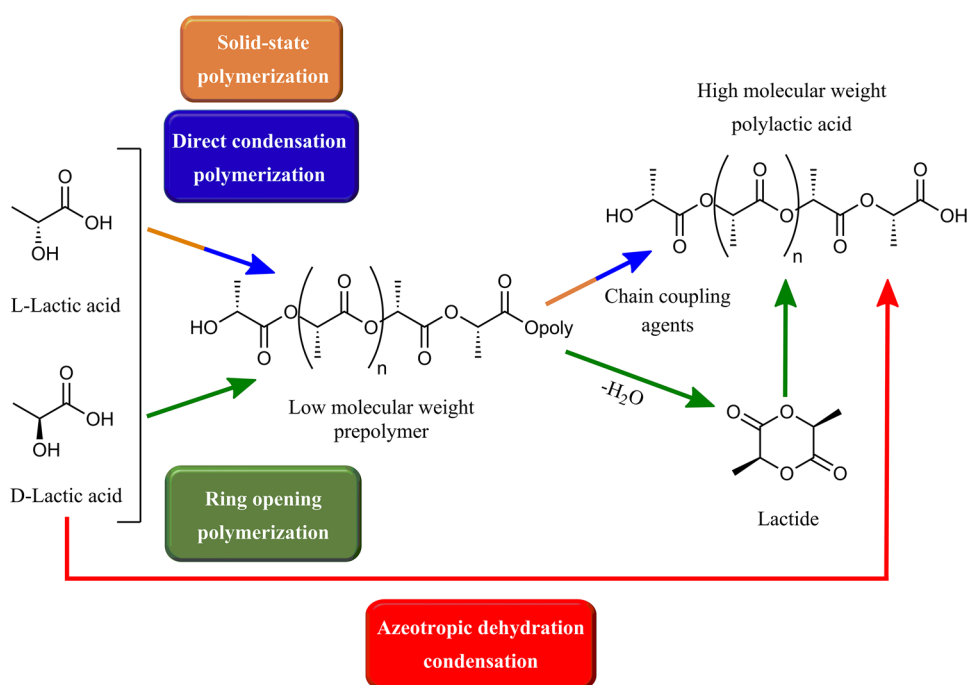
The direct polycondensation, while being a cost-effective approach to polymerize lactic acid, it faces a drawback in generating high molecular weight polymers. This method involves removing water under specific conditions. Typically, it consists of three main steps: (i) removal of free water, (ii) oligomer formation, and (iii) melt polycondensation. However, achieving a solvent-free, high molecular weight polylactic acid through this method is challenging, often requiring the incorporation of coupling agents or additives, adding complexity and cost to the process (Msuya et al. 2017; Taib et al. 2023).

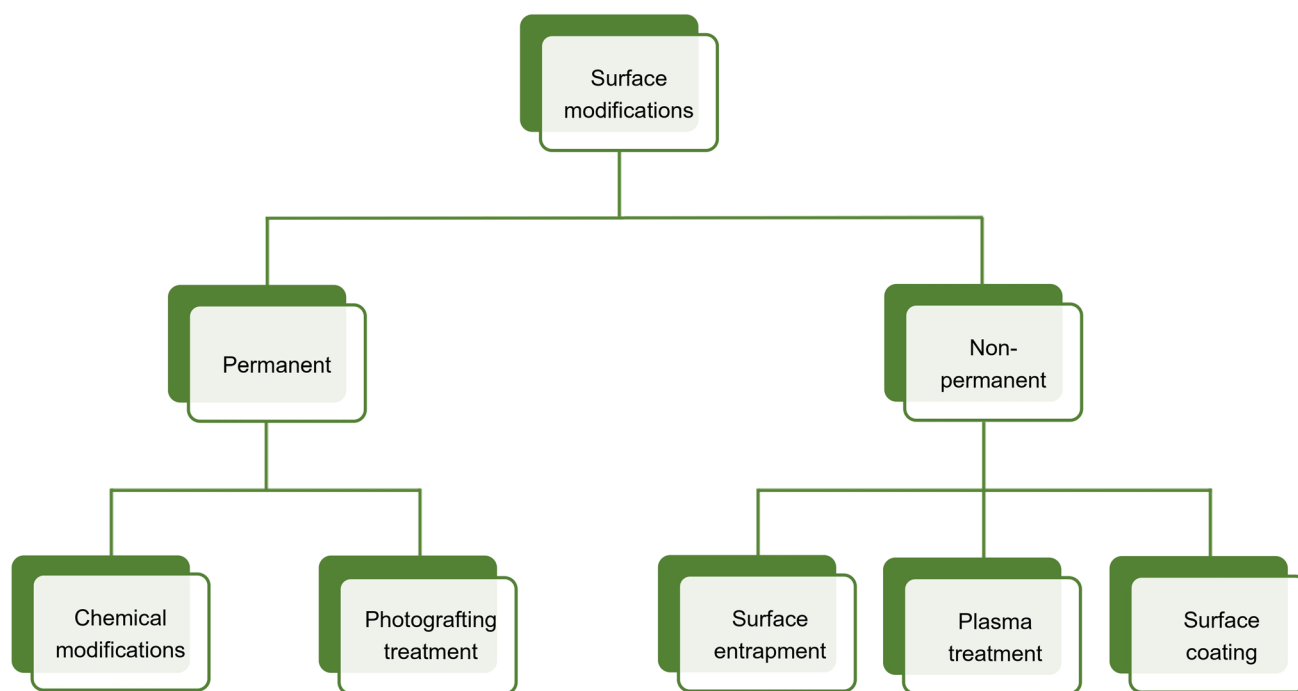
Therefore, an alternative approach to obtain high molecular weight polylactic acid is through azeotropic dehydration. This method efficiently removes water from the reaction medium, by using an organic solvent, forming an azeotrope with water without the need of chain

extenders or adjuvants (Li et al. 2020). Despite yielding high molecular weight polymers, this method introduces considerable catalyst impurities, leading to unwanted degradation, uncontrolled or unreproducible hydrolysis rates and catalyst toxicity (Msuya et al. 2017; Taib et al. 2023). On the other hand, the solid-state polymerization follows similar steps as the direct polycondensation, although it includes an additional cooling and crystallization phase after the melt polycondensation. Metals like tin, titanium, and zinc or their salts serve as suitable catalysts. This process is considered environmentally friendly because it operates at lower temperatures, avoiding side reactions, and thermal, oxidative, and hydrolytic degradation of the polymer (Vouyiouka et al. 2013; Khaptakhanova et al. 2021).

While polycondensation is the cheapest route, it is challenging to produce high molecular weight, solvent-free polylactic acid due to prolonged reaction times and solvent use. Thus, the most common route to address this is through ring-opening polymerization, which involves the conversion of lactide, the cyclic dimer of lactic acid, into polylactic acid. Firstly, the lactic acid is dehydrated at high temperatures and vacuum conditions and poly-condensed into its oligomers. Then through internal transesterification, catalytic depolymerization into lactide occurs, forming high molecular weight polylactic acid, when the lactide ring opens. This approach offers advantages, such as minimal moisture in the molten polylactic acid resin, short residence times, mild process conditions, and no byproducts, making it the preferred method for industrial-scale production (Mehta et al. 2005; Taib et al. 2023).

Fig. 1 Main synthesis methods of polymerization used in the production of polylactic acid





Scheme 1 Surface modifications methods

The versatility of polylactic acid allows it to be used in several industries and sectors, such as chemistry, medicine, pharmaceuticals, and biotechnology. However, there are some drawbacks that should be taken into consideration, namely its relatively higher cost when compared to fossil-based plastics, weaker mechanical properties, low melting point, and higher permeability, which limit its applications in the industrial field (Hu et al. 2018a). Therefore, significant efforts have been devoted to enhancing the properties of polylactic acid. One strategy employed is the introduction of bioactive compounds, leading to the development of bioactive polylactic acid materials with improved properties. Thus, the objective of this review is to provide a comprehensive overview of the current research and development in the field of bioactive polylactic acid. It aims to summarize the methods and strategies employed on the preparation of these materials, evaluating the effectiveness of these modifications. Therefore, the first part of this review focuses on the different methods and techniques used to modify the surface of polylactic acid to impart bioactive properties, while the second part discusses the incorporation of bioactive molecules into polylactic acid, highlighting their potential applications in different fields.

Surface modification

Surface modification of polylactic acid plays a crucial role in expanding its range of applications by tailoring its surface properties to specific requirements. By adding

bioactive compounds at the surface of the material, it becomes possible to create favourable interactions at the interface, improving bioavailability while maintaining the bulk properties of polylactic acid. This approach offers the added benefit of minimizing the consumption of active substances (Stoleru et al. 2021).

Several approaches can be employed to enhance the surface of polylactic acid, namely (1) permanent surface changes through covalent attachment, and (2) non-permanent modifications through non-covalent attachment (Scheme 1).

Considering the existing reviews on certain topics, our aim is to explore surface modification methods with recent applications, specifically focusing on the incorporation of bioactive compounds.

Chemical modification

Since polylactic acid is not inherently bioactive and has limited reactive groups, chemical modifications on its structure must be required. These modifications allow the attachment of other molecules, and consequently, the enhancement of the polymer for specific applications. One simple method involves alkaline hydrolysis, which results in the creation of carboxylic acids ($-\text{COOH}$) and hydroxyl ($-\text{OH}$) groups on the polylactic acid surface (Wang et al. 2005). Typically, acid groups are initially activated with phosphorous pentachloride (PCl_5), thionyl chloride (SOCl_2), or water-soluble carbodiimides and subsequently conjugated with compounds

containing amines or hydroxyl groups, expanding the potential applications of polylactic acid (Luo et al. 2004; Zhang et al. 1999; Janorkar et al. 2004).

Although alkali surface treatments have shown to be effective in improving the bioactivity of polylactic acid materials, it is important to consider their potential drawbacks. One of the main concerns is that these treatments can cause undesirable changes in the morphology of the polymer surface, affecting the overall performance and functionality of the material (Liu et al. 2012).

In order to incorporate bioactive compounds, Pan et al. (2005) initially conducted a modification of the side chain of polylactic acid, by introducing carboxyl and amino groups. This modification preserved its biodegradability and regulated its acidity during hydrolysis. This process involved a method where maleic anhydride was covalently grafted onto the side chain of polylactic acid through a free radical reaction, at a temperature of 100 °C for 20 h, using benzoyl peroxide as the initiator. Subsequently, hexanediamine was incorporated into the structure.

Therefore, chemical modifications play an essential role in enhancing the versatility of polylactic acid for specific applications by introducing reactive groups and expanding its potential functionalities.

Photografting

Photografting is a method that uses photoactivation to generate reactive groups, which are then used for grafting selected functionalities. Regarding polylactic acid, this method is extensively employed for customizing its surface properties, since it lacks readily reactable side chain groups.

Photografting stands out for its cost-effectiveness, mild reaction conditions, selectivity of ultraviolet light, and the ability to permanently change the surface chemistry, proving to be an effective way to modify the polylactic acid surface (Ma et al. 2000).

There are two types of surface grafting methods: “grafting to” and “grafting from” (Fig. 2).

In the “grafting to” approach, a molecule is attached or “grafted” onto a substrate surface. This is typically achieved through chemical reactions between functional groups on the substrate and the grafted material or via photochemical reactions. This method encounters limitations in grafting polymers or creating ultrathin coatings due to steric hindrance (Mueller et al. 2022).

In the “grafting from” approach, the polymerization or attachment of molecules occurs directly from the substrate surface. This means that the polymer chains or molecules are grown or formed directly on the surface. This method leads to higher grafting densities and film thicknesses (Mueller et al. 2022).

Zhang et al. (2019) developed a novel scaffold using the “grafting to” approach. The method consisted in soaking the polycaprolactone-polylactic acid films into a photoactive polypropylene amine for 30 min, followed by 20 min ultraviolet light photografting treatment. Insulin-like growth factor 1 and tumour necrosis factor- α were then immobilized onto the prepared scaffold using a photochemical reaction. The results indicated successful inhibition of cell senescence, induction of bone marrow mesenchymal stem cells differentiation, and biocompatibility.

On the other hand, Wang et al. (2020) explored chemical modifications through the “grafting from” approach. In this study, they demonstrated the graft-polymerization of

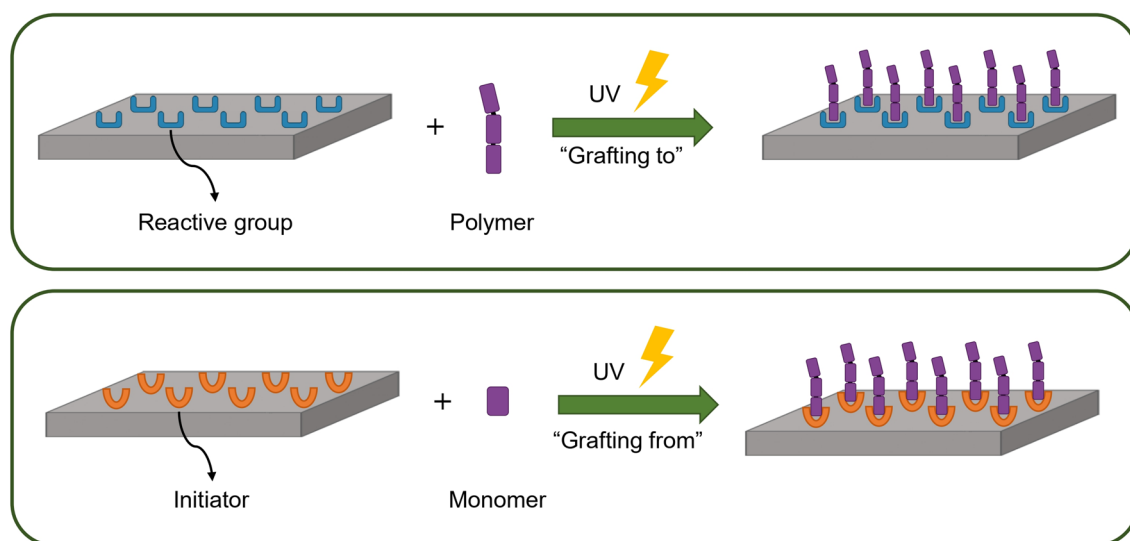


Fig. 2 The “grafting to” and “grafting from” of surface grafting methods

poly(acrylic acid) onto polylactic acid chains, using benzophenone as the photoinitiator. The photografting process achieved a high graft ratio (up to 180%) without forming unwanted homopolymers of acrylic acid. Notably, when the acrylic acid to polylactic acid graft ratio exceeded 100%, the resulting polymer could be dispersed in water, forming stable suspensions.

In a different study, Oktay et al. (2022) developed a sustained release system for paclitaxel via photografting. The method involved preparing a solution of methacryloyloxyethyl phosphorylcholine monomer. Polylactic acid nanofibre mats were then immersed in this solution and exposed to ultraviolet light radiation. The results showed that the addition of poly(methacryloyloxyethyl phosphorylcholine improved the solubility of paclitaxel. As for the nanofibre mats, it showed good biocompatibility with human umbilical vein endothelial cells, indicating non-toxicity during *in vivo* drug release.

Using a two-step approach, Karakurt et al. (2019) focused on immobilizing saccharides onto the polylactic acid surface, with the objective to impart antibacterial features. This method involved first attaching poly(acrylic acid) brushes into the surface of polylactic acid, using a plasma post-irradiation grafting technique. Subsequently, glucosamine and chondroitin sulphate were immobilized to developed films as effective bactericidal agents. The combination of these saccharides enhances cell viability, suggesting potential for medical device applications.

Regarding the 3D-printed materials, Liao et al. (2023) developed a 3D-printed polylactic acid using fused filament fabrication. The method involved treating the surfaces with atmospheric-pressure plasma followed by ultraviolet light-induced photografting polymerization of 2-hydroxyethyl methacrylate, poly(ethylene glycol) methacrylate, and hydroxyapatite. The results indicated successful hydrophilization, as shown by the water contact angle test. Additionally, the treated surfaces, when examined *in vitro* with osteoblast-like MG63 cells, demonstrated improved biocompatibility, suggesting potential applications in future bone scaffolds.

The photografting method enhances polylactic acid surface properties, offering adaptability for diverse applications, including tissue engineering and drug delivery. The “grafting to” and “grafting from” strategies showcase its effectiveness, enabling control over surface chemistry for tailoring these applications.

A summary of the bioactive compounds applied by photografting onto the surface of polylactic acid, highlighting the main changes, and the results achieved is described in Table 1.

Surface entrapment

The entrapment method is employed to incorporate molecules that do not adhere to polylactic acid. In contrast to other strategies, this method does not require readily reactive side chain groups (Quirk et al. 2000).

Quirk et al. (2000) used the entrapment method to modify the polylactic acid surface, during the reversible swelling of the polymer surface region. The study involved the physical entrapment of a second polymer, the poly(ethylene glycol), and poly(L-lysine). The presence of poly(L-lysine) provided functional amine groups for potential covalent coupling of biological ligands.

Using the same strategy, Zhu et al. (2002a) introduced a second polymer and four distinct types of alginate-amino acid derivatives into poly(DL-lactide). The objective was to mimic the glycocalyx of cell membrane in order to promote cell adhesion and growth of chondrocyte. The surface analyses confirmed the feasibility of this approach, demonstrating changes in surface chemistry, such as the enhancement of hydrophilicity.

Another study, conducted by the same research group, entrapped biomacromolecules, such as alginate, chitosan, and gelatine into poly(DL-lactide). The method involved the immersion of poly(DL-lactide) films into the biomacromolecule solutions, using a solvent that slightly swells the polymer. The swollen base polymer impregnated with biomacromolecules is removed and placed in a non-solvent, causing the collapse of the base polymer, entangling biomacromolecules at the surface (Fig. 3). The modified films exhibited enhanced hydrophilicity and the formation of a surface physical interpenetrating network layer, between the biomacromolecules and the poly(DL-lactide) film (Zhu et al. 2002b).

Regarding recent studies, a different approach was conducted by Tang et al. (2017). They developed an innovative extraction method for the preparation of hydrophobic ion-pairing-colistin, using different water-insoluble anionic lipids. The focus was on enhancing the entrapment of therapeutic peptides, specifically colistin, within polylactic acid nanoparticles, and studied its loading and release process.

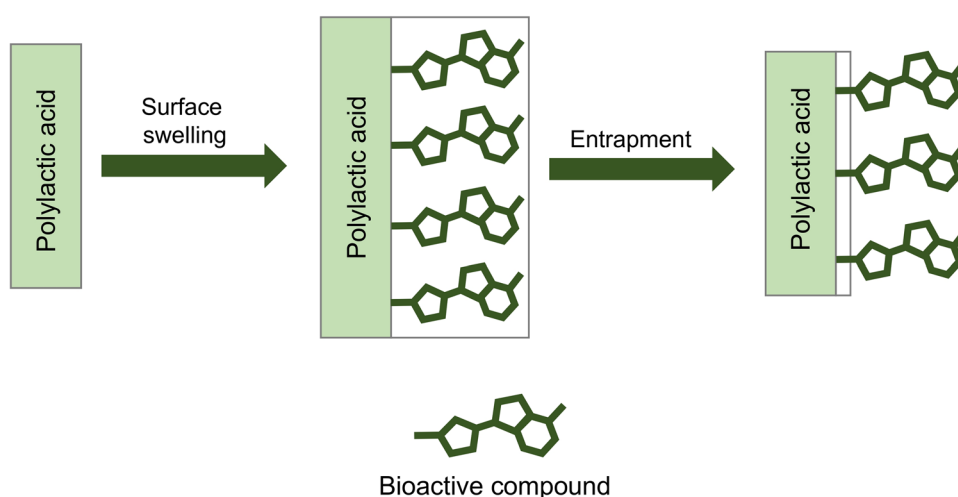
Using the 3D-printed polylactic acid scaffolds, Wang et al. (2019) modified its surface by integrating chitosan via surface entrapment method. This approach involved dipping the polymer into a chitosan solution and then submerging it in an excess of a nonsolvent solution, in order to trap the biomacromolecules on its surface. The results showed that *in vitro* mineralization chitosan played a key role in promoting the hydroxyapatite growth. Furthermore, in cell culture studies, the scaffold exhibited high cell viability, suggesting that this modification was biocompatible towards human fibroblast cell.

Table 1 Bioactive compounds applied by photografting on the surface of polylactic acid

Bioactive compounds	Method	Changes on polylactic acid after treatment	Main results	References
Insulin-like growth factor 1 and tumour necrosis factor- α	Photografting treatment	Good thermal stability and smoother surface texture	Inhibition of cell senescence Improved biocompatibility and differentiation of bone marrow mesenchymal stem cells	Zhang et al. (2019)
Poly(acrylic acid)*	Photografting treatment	The graft ratio increased with increasing irradiation time	Increased water dispersibility with higher grafting ratios Potential used as a compatibilizer in blending polylactic acid with other materials	Wang et al. (2020)
Poly(methacryloyloxyethyl phosphorylcholine)*	Photografting treatment	Did not alter significantly the morphological structure of polylactic acid nanofibres	Improved the solubility of paclitaxel and biocompatibility with human umbilical vein endothelial cells	Oktay et al. (2022)
Glucosamine and chondroitin sulphate	Two-step approach: plasma treatment followed by photografting	Enhancement of surface roughness and hydrophilicity	Exhibited high antimicrobial activity Improved biocompatibility, with high cell viability	Karakurt et al. (2019)
Hydroxyapatite	Two-step approach: Plasma treatment followed by photografting	Enhancement of surface hydrophilicity	Improved cell adhesion and growth of osteoblast-like MG63 cells	Liao et al. (2023)

*Poly(acrylic acid) is a synthetic polymer that can be utilized in bio-related applications, taking advantage of its physicochemical properties

*Poly(methacryloyloxyethyl phosphorylcholine) is a biocompatible polymer

Fig. 3 The entrapment method, through swelling of the polymer

On the other hand, Smruthi et al. (2022) evaluated the optimized nanoformulation of naringenin entrapped in two different polymers, polylactic acid and polyvinyl alcohol. Entrapped naringenin in polylactic acid/polyvinyl alcohol showed improved antioxidant activity and sustained patterns release in vitro, exhibiting higher bioaccessibility in simulated gastrointestinal conditions. Studies in vivo revealed

higher relative bioavailability in rats compared to free suspension, with enhanced absorption, prolonged circulation, and increased accumulation, especially in the liver.

Overall, the entrapment method provides tailored solutions without the need to introduce new chemical groups. Its adaptability holds promise for advancing biomedical and

pharmaceutical applications, showcasing their broad potential in material engineering.

A summary of the bioactive compounds entrapped onto the surface of polylactic acid, highlighting the main changes, and the results achieved is described in Table 2.

Plasma surface treatment

Plasma treatment is a widely studied technique for modifying the surface chemistry of the materials while preserving its bulk properties. Unlike alkali surface treatments, plasma treatment does not significantly alter its morphology or mechanical properties (Jacobs et al. 2012). Basically, this method involves exposing a material to an ionized gas known as plasma. This plasma, generated by an energy source, is composed of electrons, ions, metastatic ions, and free radicals. When the material's surface is exposed to it, the activated species interact with the surface breaking up molecular chains and creating new functional groups (Abdulkareem et al. 2021).

Since the 1960s, the field of materials surface modification by plasma treatment has undergone an enormous expansion. Much of this has taken place in recent years, particularly in the surface modification of polymeric materials, namely polylactic acid, for which exist numerous industrial applications (Rasal et al. 2010). In relation to polylactic acid, there has been a growing interest in using plasma treatment to enhance its surface hydrophilicity and cell affinity.

A study developed by Nakagawa et al. (2006) showed that plasma treatment is a technique used to modify the surface of the material by adding functional groups like carboxyl and hydroxyl, making it more attracted to water. The results indicated an enhancement in polylactic acid surface hydrophilicity, evidenced by a reduction in the water contact angle. This modification had a positive impact on the biological performance of the scaffolds as it improved the capacity of cells to adhere to the surface.

Similarly, Jordá-Vilaplana and coworkers (2014), increased the surface hydrophilicity of polylactic acid by using this technique. Moreover, they also observed changes in the topography of the polymer surface, resulting in an enhancement of its roughness.

More recently, Filippova et al. (2020) investigated the impact of implanting plasma-modified polylactic acid films into the eyes of 12 female rabbits, focusing on corneal morphology. After 21 days, the samples revealed a mild inflammatory response, marked by leucocyte infiltration, new blood vessels, altered collagen fibres, and the presence of sulphated glycosaminoglycans. More importantly, intraocular pressure remained unaffected, suggesting potential use for these films as future corneal implants.

Regarding the incorporation of bioactive compounds within the polylactic acid surface with biomedical applications, Abdulkareem et al. (2021) explored its surface modification by incorporating two antimicrobial agents, ascorbic and fumaric acids. This modification resulted in increased

Table 2 Bioactive compounds entrapped on the surface of polylactic acid

Bioactive compounds	Method	Changes on polylactic acid after treatment	Main results	References
Poly(L-lysine)	Surface entrapment	Poly(L-lysine) provided functional amine groups for potential covalent coupling of biological ligands	Suitable for tissue engineering applications	Quirk et al. (2000)
L-lysine, L-arginine, L-aspartic acid, and L-phenylalanine	Surface entrapment	Enhancement of surface hydrophilicity	Improved chondrocyte attachment and proliferation	Zhu et al. (2002a)
Alginate, chitosan, and gelatine	Surface entrapment	Enhancement of surface hydrophilicity Formation of a surface physical interpenetrating network layer	Potential for applications in drug delivery, implanted devices, and tissue engineering	Zhu et al. (2002b)
Colistin	Surface entrapment	Exhibited swelling in foetal bovine serum Decreased of critical aggregation concentration, implying an improvement in thermodynamic stability	Potential for drug delivery systems	Tang et al. (2017)
Chitosan	Surface entrapment	Decreased of the compressive modulus Enhancement of surface hydrophilicity	Promotes the hydroxyapatite growth Biocompatible towards human fibroblast cell	Wang et al. (2019)
Naringenin	Surface entrapment	Changes in particle size depending on the formulation The surface charge decreased	Improved antioxidant effectiveness, prolonged release, and bioavailability	Smruthi et al. (2022)

wettability, which contributed to improved adhesion characteristics, allowing for better bonding of the polylactic acid to other surfaces or materials. Plasma treatment not only enhance cell adhesion and proliferation, but also have a significant impact on cell morphology.

More recently, a two-step strategy was employed to turn polylactic acid into a bioactive material without compromising its inherent properties. Aflori et al. (2019) introduced a two-step method to produce poly(L-lactide)/chitosan-silver nanoparticles scaffolds. The process involved plasma treatment applied for 4 and 10 min at 30 W, increasing the surface roughness, followed by wet chemical treatment of poly(L-lactide) films in a chitosan-based silver nanoparticles solution. The results demonstrated high biocompatibility with pre-osteoblastic cell line and antimicrobial activity.

Hu and coworkers (2018b) improved the surface properties of polylactic acid films, using cold plasma treatment to facilitate the coating of nisin on its surface. In comparison to the untreated polymer film, polylactic acid-nisin significantly reduced the total viable count of *Listeria monocytogenes*.

With similar results, Huang et al. (2020) modified polylactic acid using plasma treatment to covalently attached antibacterial agents. The treatment induced surface coarseness, and increased hydrophilicity by introducing carboxylic acid groups on the polymer films, to covalently attached the nisin or ϵ -poly lysine. The resulting films exhibited effective bacterial inhibition (*Staphylococcus aureus*), and extended shelf life of fresh beef during cold storage.

For the same purpose, Chen et al. (2020) enhanced zein films through the cold plasma treatment, followed by coating with porous polylactic acid. This modification increased surface hydrophobicity, tensile strength, and water vapor barrier, while maintaining biodegradability. Furthermore, the films showed high ultraviolet light barrier, making them suitable for biodegradable packaging.

In 2023, the same authors explored the impact of dielectric barrier discharge cold plasma technology on enhancing the properties of polylactic acid films. The application of different plasma power during treatment increased surface roughness and polar functional groups, enabling the chitosan coating. The resulting films displayed antimicrobial activity against *Staphylococcus aureus*, indicating their potential for food packaging (Chen et al. 2023).

In addition to air, other gases can be used for plasma treatment to functionalize the surface of the samples. Luque-Agudo et al. (2021) conducted a study exploring the impact of argon and oxygen plasma on polylactic acid films deposited on titanium, focusing on the nature and duration of the surface changes. The conditions were the same in both experiments: a power range of 0–24 W, a frequency of 100 kHz, a treatment time of 10 min, and a gas pressure of 0.5 bar. The results showed that both plasmas induced similar roughness and increased hydrophilicity; however, the

effect was more enduring with argon treatment, due to the lower mobility of the chains.

Laput and coworkers (2019) used the argon plasma treatment to develop a polylactic acid and polylactic acid/hydroxyapatite composite in a 70/30 ratio. The method involved subjecting samples to the treatment with varying exposure times (3.5, 7, and 10.5 min). The results showed an increased crystallinity of polylactic acid and composites after the method, due to polymer chain disruption, as well as enhanced wettability, contributing to improved adhesion properties for potential biomedicine applications.

Despite effectively enhancing polylactic acid wettability and cell affinity, plasma treatment faces challenges due to the partial loss of effectiveness over time. This drawback is attributed to surface rearrangement, where thermally activated macromolecular motions attempt to minimize interfacial energy, causing the modified surface to gradually revert to its original state. This non-permanent effect poses a challenge for long-term stability and reliability (Rasal et al. 2010). Moreover, increased plasma power and treatment time can lead to an increase in degradation of the polymer, impacting its physical, chemical, mechanical, and thermal properties (Antunes et al. 2021). Therefore, these limitations may restrict the broad applicability of plasma treatment.

A summary of the bioactive compounds applied by plasma treatment onto the surface of polylactic acid, highlighting the main changes, and the results achieved is described in Table 3.

Surface coating

Surface coating refers to the process of depositing or adsorbing a modifying substance onto the surface of a polymer. It is a straightforward and convenient method of surface modification. However, one drawback of coating is that the passive adsorption can lead to competitive adsorption of other materials present in the system, changing the configuration of the adsorbed species (Wang et al. 2005; Rasal et al. 2010).

Regarding bioactive compounds, numerous studies have used the coating process to incorporate these compounds onto polylactic acid surfaces, aiming to impart specific functionalities and properties to the material. Polylactic acid has found significant relevance in a wide range of medical applications, including tissue engineering, regenerative medicine, cardiac, drug carrier, among others. Its inherent features make it particularly suitable for rapid prototyping and efficient manufacturing using 3D printing technology. This capability enables the production of patient-specific tissue engineering scaffolds, where polylactic acid constructs can be tailored to match individual anatomical requirements (DeStefano et al. 2020).

Kao et al. (2015) improved human adipose-derived stem cell behaviour by coating the 3D printed scaffold surface

Table 3 Bioactive compounds applied by plasma treatment on the surface of poly(lactic acid)

Bioactive compounds	Method	Changes on poly(lactic acid) after treatment	Main results	References
<i>Biomedical applications</i>				
–	Plasma treatment	Enhancement of surface hydrophilicity	Improvement of cell adhesion of pre-osteoblastic cell line	Nakagawa et al. (2006)
–	Plasma treatment	Enhancement of surface roughness and hydrophilicity	Good adhesion properties	Jordá-Vilaplana et al. (2014)
–	Plasma treatment	Reduced surface roughness and enhanced hydrophilicity and surface energy	The plasma-modified poly(lactic acid) after implantation displayed biocompatibility, mild inflammatory response, and stable intraocular pressure	Filippova et al. (2020)
Ascorbic and fumaric acid	Two step approach: plasma treatment followed by grafting reactions	Enhancement of surface roughness and wettability Increased total surface free energy and polar components	Improved cell adhesion and proliferation	Abdulkareem et al. (2021)
Chitosan	Two step approach: plasma treatment followed by wet chemical treatment	Enhancement of surface roughness, wettability, and surface energy	Modified poly(L-lactide) films showed high biocompatibility, enhanced cell adhesion, and proliferation of pre-osteoblastic cell line	Aflori et al. (2019)
Hydroxyapatite	Plasma treatment	Longer plasma exposure increased oxygen and decreased carbon atoms content Enhanced crystallinity, surface porosity, and wettability	Improved cell adhesion	Laput et al. (2019)
<i>Packaging applications</i>				
Nisin	Plasma treatment followed by coating	The thermal properties remained unchanged It initially raised, then reduced surface roughness, impacting hydrophilicity	Exhibited antimicrobial activity against <i>Listeria monocytogenes</i>	(Hu et al. 2018b)
Nisin and ϵ -poly lysine	Two step approach: plasma treatment followed by grafting reactions	Increased surface roughness, carboxyl group concentration and protein content	Inhibition of bacterial and microbial growth	Huang et al. (2020)
Zein	Two step approach: plasma treatment followed by coating	The films exhibited well-ordered porous structure and good optical transparency Enhancement of surface hydrophobicity, tensile strength, water vapor barrier, and thermal stability	Improved UV barrier and biodegradability, making the films suitable for biodegradable packaging	Chen et al. (2020)
Chitosan	Plasma treatment	Enhancement of surface roughness, hydrophilicity and crystallinity The films exhibited higher elongation at break and tensile strength	Exhibited antimicrobial activity against <i>Staphylococcus aureus</i>	Chen et al. (2023)

with polydopamine. The deposition of dopamine into the polymer increased the carbon and nitrogen while decreasing oxygen content. As a result, the polylactic acid scaffolds became highly hydrophilic, enhancing the cell adhesion and subsequently promoting cell proliferation and differentiation.

A similar study was conducted by Nazeer et al. (2020) who introduced chitosan and hydroxyapatite on the surface of 3D-printed polylactic acid scaffolds. This modification improved the hydrophilicity and bioactivity of the material, exhibiting enhanced attachment and proliferation of human osteosarcoma cells in vitro.

Saniei et al. (2020) successfully used electrospinning to coat polylactic acid screw implants with poly(vinyl alcohol)-nanohydroxyapatite nanofibres. This study revealed that the introduction of nanohydroxyapatite accelerated the formation of an appetite layer on the screw surfaces. This fast mineralization led to an increase of the surface roughness, promoting improved cell adhesion and growth of MC3T3-E1 cells.

With similar results, Grigora et al. (2023) applied bioactive coatings, such as mesoporous strontium bioglass and strontium bioglass combined with nanohydroxyapatite on 3D-printed polylactic acid/montmorillonite nanocomposite scaffolds. It improves their hydrophilicity, biomineralization and promotes the differentiation of stem cells into osteoblasts.

On the other hand, Lett et al. (2020) explored the antibacterial efficacy of a poly(vinyl alcohol)-bound silver-hydroxyapatite composite coated on the polylactic acid scaffold. This study revealed enhanced crystallinity and smaller crystallite size as hydroxyapatite is doped with silver. Additionally, the scaffold displayed antibacterial efficacy, in vitro, hemocompatibility, and bending strength comparable to cortical bone, indicating potential for bone tissue regeneration.

In a different study, Zhang and coworkers (2022) enhanced the 3D polylactic acid scaffold by coating it with exosomes from mesenchymal stem cells. The study showed that the incorporation of exosomes significantly improved the bio-functionality of the scaffold, as demonstrated by a notable decrease in pro-inflammatory markers and reactive oxygen species in inflammatory macrophages. Furthermore, in vitro osteogenesis studies indicated elevated expression of osteoblastic markers and mineralization, highlighting the pro-osteogenic effects of the bioactive 3D porous polylactic acid scaffold.

Using a two-step method, Miletić et al. (2020) functionalized the polylactic acid by coating antiseptic and anti-inflammatory nanostructured systems based on chitin–lignin complexes. Since coating showed minimal impact on their properties, this methodology provides a promising method for diverse applications, balancing thermo-mechanical, and functional properties in potential skin-contact applications.

In overall, this surface modification approach holds potential for enhancing the bioactivity and cell affinity of polylactic acid implants, thus contributing to their efficacy in biomedical applications.

Coating polylactic acid films for packaging applications aims to address the inherent limitations of polylactic acid, such as its poor gas barrier and antibacterial properties, by improving its functionality to better preserve the freshness and quality of food products. Therefore, several studies were conducted with this aim.

Stoleru et al. (2021) demonstrated that by applying a coating of chitosan-clove essential oil or chitosan-argan vegetal oil onto polylactic acid films provided ultraviolet protection, antioxidant and antimicrobial properties. This approach presents a convenient method for food packaging, since it ensures bacterial inhibition on the coated side while maintaining polylactic acid's biodegradability on the uncoated side.

Similarly, Fiore et al. (2021) applied a coating of chitosan or chitosan-caseinate blend enriched with rosemary essential oil onto polylactic acid films. This coating showed effective antioxidant properties when used in the packaging of fresh meat products, offering a viable solution for improving product quality and prolonging the shelf life of the packaged.

By addressing a different subject, Darya et al. (2022) focused on the challenge of reducing the toxic effects of common biocides in marine environments and developing eco-friendly natural antifouling coatings. The researchers tested the antifouling activities of nine bioactive extracts from different organs of the sea cucumber *Stichopus herrmanni*. Based on the results, an ethyl acetate extract was selected and added to coatings composed of polycaprolactone/polylactic acid blends with different polylactic acid compositions. The findings revealed the antibacterial and antifouling potential of semi-polar bioactive extracts from the body wall of *Stichopus herrmanni* as natural antifoulants.

On the other hand, Benito-González et al. (2020) developed lightweight, hydrophobic adsorbent pads using aerogels derived from various cellulosic and nanocellulosic fractions extracted from *Posidonia oceanica* waste biomass. This study showed that the introduction of polylactic acid enhanced the hydrophobicity. Additionally, all aerogels prepared adsorbed larger amounts of oil, suggesting potential applications in oil spill cleanup and food packaging as efficient adsorbent pads.

In other studies, researchers have developed polylactic acid multilayer active films using a dual-coating technique to improve their active packaging functions and gas barrier properties. This approach involves applying two distinct coatings onto the polylactic acid base film. The first coating, often composed of bioactive compounds, is applied to provide the main active packaging functions, while the second coating is typically designed to further

enhance the active packaging functions and improve barrier properties of the film (Mao et al. 2022, 2023; Wang et al. 2023).

Keeping this in mind, the same research group successfully developed several types of polylactic acid multilayer active films. In these experiments, the first coating is composed of proanthocyanidin/poly(vinyl alcohol), chitosan/poly(vinyl alcohol), and anthocyanin/poly(vinyl alcohol), while the second coating is composed of proanthocyanidin, quercetin, and anthocyanin functionalized layered double hydroxides, respectively. In general, all the active films exhibit improved ultraviolet barrier, oxygen barrier, antioxidant, and antibacterial properties, leading to an extension in the shelf life of packaged products (Mao et al. 2022, 2023; Wang et al. 2023).

The extensive range of coating techniques in incorporating bioactive compounds and addressing specific limitations, underscores the potential of surface coating to enhance polylactic acid's functionalities, making it a promising material for diverse and innovative purposes in biomedicine and sustainable packaging.

A summary of the bioactive compounds that have been coated onto the surface of polylactic acid, highlighting the main changes and the results achieved is described in Table 4.

Incorporation of bioactive compounds

The incorporation of bioactive compounds refers to a technique in which the compounds have interaction with polylactic acid and do not require reactive side chain groups for attachment. There are several methods available for incorporating bioactive compounds in polylactic acid, depending on the nature of the compound, the desired distribution within the polylactic acid matrix, the compatibility with polylactic acid and the final application requirements.

In the following section, a detailed description of some commonly used incorporation methods will be provided as well as its limitations and recent studies illustrating their practical applications (Scheme 2).

Encapsulation

The encapsulation method provides a means to enhance the properties and efficacy of bioactive compounds by incorporating them into biodegradable polymers, such as chitosan and polylactic acid (Schaefer et al. 2020). This technique improves solubility, enables controlled release, and provides a surface for ligands, facilitating targeted delivery (Kumari et al. 2010b).

Bioactive compounds can be encapsulated within polylactic acid nanoparticles by either attaching them to the nanoparticles matrix or directly adding them encapsulated into the solutions used to form the films. This technique not only safeguards bioactive molecules from degradation but also extends their longevity, providing versatile approaches with applications in different fields including food packaging, tissue engineering, drug delivery, bioimaging, and biosensing (Ferreira Nogueira et al. 2019; Kumar et al. 2019; Bhatia et al. 2023; Sunil 2012).

In the encapsulation process, the emulsification-solvent evaporation method is widely used (Fig. 4) (Sousa et al. 2019). Kumari et al. (2010a) showed that quercetin could be successfully encapsulated within polylactic acid nanoparticles using the solvent evaporation method. The results showed that, remarkably, the antioxidant activities of the nanoparticles were comparable to those of free quercetin. Moreover, the encapsulation improved the aqueous solubility and stability of quercetin, underlining the potential of using polylactic acid to encapsulate highly active antioxidant molecules and develop improved therapeutic compounds.

Using the same technique, Ochieng et al. (2021) prepared curcumin nanoparticles encapsulated in polylactic acid. The results showed that higher sonication amplitude and a 5 min sonication time reduced significantly the nanoparticle size. The optimal conditions were found with 0.2 mg/mL curcumin concentration and 400 mg of dimethylamine borane at 100 μm , resulting in ideal polydispersity index, average hydrodynamic diameter, zeta potential, and encapsulation efficiency values.

Additionally, versatile spray drying and nanoprecipitation methods have been reported as significant techniques for the production of polylactic acid nanoparticles (Fig. 4) (Hong et al. 2018; Arpagaus 2019). Blanco et al. (2005) encapsulated 5-fluorouracil within polylactic acid microspheres, using the spray-drying method. The resulting drug-loaded particles exhibited an average diameter of 1.1–1.7 μm , making them suitable for numerous biological applications. The small size of nanoparticles enables them to easily penetrate barriers and reach specific cells, facilitating efficient drug delivery.

On the other hand, Assunção et al. (2021) by using the nanoprecipitation technique, successfully encapsulated carotenoid extract from *Spirulina* sp. LEB 18, using polylactic acid/poly(DL-lactic-co-glycolic) acid (75:25 w/w) as an encapsulant. The resulting nanoparticles showed high homogeneity and thermal stability, highlighting its potential for improved carotenoid delivery in several applications.

Related to drug delivery applications, Buhecha et al. (2019) co-encapsulated theophylline and budesonide in polylactic acid nanoparticles for pulmonary drug delivery. The polylactic acid nanoparticles were produced using a double emulsification solvent diffusion method and assessed

Table 4 Bioactive compounds applied as coatings on the surface of polylactic acid

Bioactive compounds	Method	Changes on polylactic acid after treatment	Main results	References
<i>Biomedical applications</i>				
Polydopamine	Coating	Enhancement of surface smoothness and hydrophilicity	Improvement on cell adhesion, proliferation, and differentiation of human adipose-derived stem cells	Kao et al. (2015)
Chitosan and Hydroxyapatite	Coating	Enhancement of surface smoothness and hydrophilicity	Improvement on cell adhesion and proliferation of human osteosarcoma cells	Nazeer et al. (2020)
Hydroxyapatite	Coating by electrospinning	Enhancement of surface roughness and hydrophilicity	Improvement on cell adhesion and growth of MC3T3-E1 cells	Saniei et al. (2020)
Strontium bioglass and hydroxyapatite	Two step approach: alkali surface treatment followed by coating	Enhancement of surface smoothness and hydrophilicity Improved mechanical properties, such as hardness and elasticity	Improved biomineralization and promote the differentiation of stem cells into osteoblasts	Grigora et al. (2023)
Hydroxyapatite	Coating	The scaffold displayed an open-porous structure, crucial for tissue regeneration	Improved the biocompatibility and antibacterial efficacy	Lett et al. (2020)
Exosomes	Coating	Increased the bending strength The coating contributed to the creation of a bioactive 3D porous structure in the polylactic acid scaffold	The scaffold demonstrated an immunoregulatory role Exhibited improvements in cell viability, proliferation, and osteogenic differentiation of human bone marrow mesenchymal stem cells	Zhang et al. (2022)
Chitin and lignin	Two step approach: “grafting from” method followed by coating	Improved transparency and enhanced crystallinity, tensile strength, and elasticity	Coating maintains polylactic acid properties, having potential in skin-contact applications	Miletić et al. (2020)
<i>Packaging applications</i>				
Clove essential oil and argan vegetal oil	Two step approach: plasma treatment followed by coating	Enhancement of surface hydrophilicity and UV protection	Improved the ability to inhibit microbial growth and prevent food oxidation	Stoleru et al. (2021)
Rosemary essential oil	Coating	Increased the tensile strength of the polylactic acid film with the number of layers Decrease the hydrophilic nature of the film	Improved the antioxidant effects	Fiore et al. (2021)
Extracts from organs of <i>Stichopus hermanni</i>	Coating	Enhanced the antifouling activities	Improved the antibacterial and anti-fouling potential	Darya et al. (2022)
Extracts from <i>Posidonia oceanica</i> waste biomass	Coating	Enhanced hydrophobicity and mechanical strength	Adsorbed larger amounts of oil, being efficient as adsorbent pads	Benito-González et al. (2020)

Table 4 (continued)

Bioactive compounds	Method	Changes on polylactic acid after treatment	Main results	References
Proanthocyanidin	Dual-coating	Enhanced hydrophobicity, stability, and gas barrier properties	Improvement of antioxidant and antibacterial properties	Wang et al. (2023)
Quercetin	Dual-coating	Showed good transparency and mechanical properties Enhanced UV barrier and gas barrier properties	Improvement of antibacterial properties	Mao et al. (2022)
Anthocyanin	Dual-coating	Showed good light transmittance Enhanced UV barrier and gas barrier properties	Improvement of antioxidant and antibacterial properties	Mao et al. (2023)

for size, zeta potential, drug loading, release, cell compatibility, and deposition after nebulization. The results showed that sustained drug release, low cytotoxicity, and effective nebulization make these nanoparticles a promising therapeutic strategy for pulmonary drug delivery.

Regarding packaging applications, Rusková and coworkers (2023) studied the encapsulation of lemongrass and oregano essential oils in a polylactic acid/polyhydroxybutyrate/acetyl tributyl citrate blend film for their antimicrobial and antioxidant properties evaluation. The polymer blend was prepared by melt mixing, and the essential oils were directly added to the mix. Afterwards, the resulting solutions were transformed into nanofibrous materials by electrospinning. The resulting bioactive packaging films were found to effectively maintain strawberry quality and extend shelf-life, with the film with 5% lemongrass showing a slight advantage over the film with 5% oregano.

In cosmetics, Kesente et al. (2017) encapsulated olive leaf extract into polylactic acid nanoparticles, using nanoprecipitation. The nanoparticles were characterized for size, morphology, thermal properties, and encapsulation efficiency. They exhibited anionic potential, with mean size of 246.3 nm and an encapsulation efficiency of 49.2%. The loaded nanoparticles were incorporated in a cosmetic formulation, demonstrating improved stability compared to the pure extract, including viscosity, pH, and organoleptic characteristics.

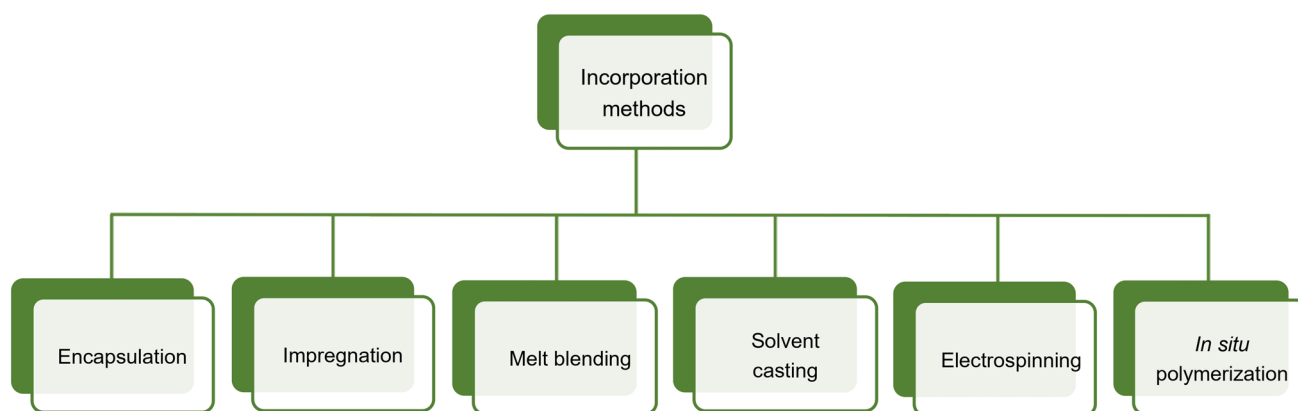
In conclusion, the encapsulation enables controlled release and targeted delivery, showcasing its potential across diverse fields including drug delivery, tissue engineering, and food packaging.

A summary of the bioactive compounds that have been encapsulated into the polylactic acid matrix, highlighting the main changes, and the results achieved is described in Table 5.

Impregnation

The impregnation process involves a supercritical fluid-assisted impregnation unit to deposit the bioactive substance into the polymer matrix, through physical or chemical interactions. Once the polylactic acid comes into contact with the bioactive compound, the carrier fluid is completely removed under reduced pressure. Several factors, such as the ratio of polylactic acid/carrier fluid/bioactive substance as well as the pressure, temperature, and contact time, play an important role in influencing the effectiveness of this method.

While there are numerous applications of the impregnation process in polylactic acid, this review will only focus on representative uses, including its application in food packaging, biomedical contexts, and as for 3D printing filament materials.



Scheme 2 Common incorporation methods

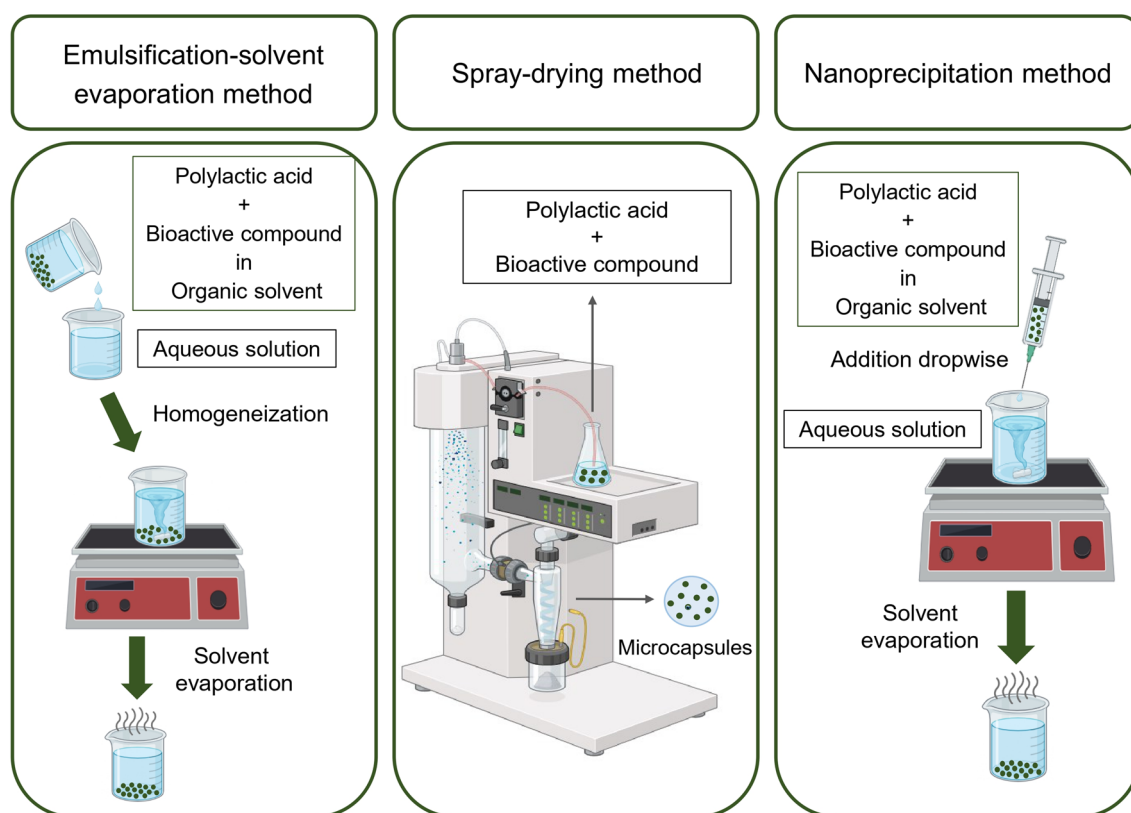


Fig. 4 Encapsulation methods. Created with BioRender.com

Several studies have employed carbon dioxide as the carrier fluid in the impregnation process of polylactic acid (Milovanovic et al. 2019). Villegas et al. (2019) used a polylactic acid/organo-modified montmorillonite C30B bionanocomposites as matrix for the impregnation of thymol and cinnamaldehyde, using supercritical carbon dioxide. The results showed changes in structural, thermal and mechanical properties, exhibiting strong antibacterial

activity, highlighting the potential for applications in fruit packaging and food preservation.

In a similar study, Lukic et al. (2020) reported the impregnation of thymol and carvacrol into polylactic acid-based films using supercritical carbon dioxide for active food packaging. This method allowed for a homogeneous distribution of thymol and carvacrol within the polylactic

Table 5 Encapsulation of bioactive compounds in polylactic acid

Bioactive compound	Method	Changes on polylactic acid after treatment	Main results	References
<i>Biomedical applications</i>				
Quercetin	Solvent evaporation method	Decreased average size Nanoencapsulation efficiency of 96.7%	Maintained the antioxidant activity Improved aqueous solubility and stability of therapeutic compounds	Kumari et al. (2010a)
5-Fluorouracil	Spray-drying technique	The microspheres exhibited a small size with a smooth and slightly porous surface	Improved penetration barriers to reach specific cells	Blanco et al. (2005)
Carotenoid extract from <i>Spirulina</i>	Nanoprecipitation technique	High homogeneity, and thermal stability Encapsulation efficiency of 88.58%	Enhanced the potential applications in carotenoid delivery	Assunção et al. (2021)
Theophylline and budesonide*	Double emulsification solvent diffusion method	Exhibited a porous and smooth surface	Sustained drug release, low cytotoxicity, and effective nebulization	Buhecha et al. (2019)
<i>Packaging applications</i>				
Curcumin	Emulsion evaporation method and ultrasonication	The properties of the nanoparticles prepared had a polydispersity index of 0.221 ± 0.048	Enhanced the bioavailability, stability	Ochieng et al. (2021)
Oregano and lemongrass essential oils	Melt mixing, encapsulation, and electrospinning	Increased in fibre diameters and porosity of the membranes Decreased of the thermal stability	Reduced microbial growth Maintain strawberry quality and extend shelf-life	Rusková et al. (2023)
<i>Cosmetics</i>				
Olive leaf extract	Nanoprecipitation	Improved stability and controlled release properties	Improved antioxidant activity	Kesente et al. (2017)

*Budesonide is a synthetic pregnane steroid, itself is not typically considered a bioactive compound. Although it is an element that when incorporated in materials can enhance bioactive properties

acid film by forming hydrogen bonds with polylactic acid, leading to an improvement in their antioxidant activity.

With the same purpose, Miranda-Villa et al. (2022) explored the use of impregnated polylactic acid films with *R*-(-)-carvone, a natural compound with antimicrobial and insecticidal properties, aiming to create a bioactive packaging material. The study examined the impact of three process variables (carbon dioxide density, temperature, and depressurization rate) on impregnation yield and carvone diffusivity. The results revealed that temperature enhanced loading, while carbon dioxide density and depressurization rate reduced it, with the highest carvone loading reaching 30%.

Regarding the use of plant extracts, Ardestani et al. (2022) impregnated bioactive compounds extracted from *Zataria multiflora* Boiss. into polylactic acid films using supercritical carbon dioxide. The results of the study indicated that the extracts obtained from the aerial parts of *Zataria multiflora* exhibited both antioxidant and antibacterial properties.

Consequently, the impregnated polylactic acid film samples showed strong antibacterial activity.

In a different study, Rosales et al. (2021) prepared 3D printing polylactic acid filaments impregnated with ethanolic mango leaves extract with pharmacological properties. The analysis of the impregnated filaments showed that they had 11.07% anti-denaturant capacity and 88.13% antioxidant activity. After the printing process, the results indicated that the bioactive properties of the impregnated filaments persisted, suggesting great potential to be used as feed materials for 3D printers.

In the same line of work, Verano-Naranjo et al. (2023) investigated the application of 3D printing in biomedicine, by impregnation of olive leaf extract into polylactic acid filaments, through supercritical carbon dioxide. They examined the impact of the printing temperature and speed on the antioxidant activity of the printed devices. The results indicated that higher temperatures had a more pronounced effect on the bioactivity of these materials, leading to a reduction in antioxidant activity, in comparison to the printing speed.

Although the potential of supercritical carbon dioxide-assisted impregnation has been highlighted in several studies, alternative fluids carriers, such as air and nitrogen have been also reported for the same purpose. Schroepfer et al. (2020) impregnated polylactic acid films with fluorine using a mixture of nitrogen or air at pressures up to 550 mbar. Gas-phase fluorination led to the formation of C–F bonds within the polylactic acid structure, resulting in a shift towards a more hydrophilic and polar surface. As a result, the fluorination process effectively modified the polylactic acid surface properties, making it more favourable for cellular interactions, improving biocompatibility and biological performance.

In conclusion, the studies highlighted the efficacy of supercritical carbon dioxide in impregnating polylactic acid with various bioactive agents, including antimicrobial compounds and plant extracts, showcasing the potential for creating functional materials with enhanced properties for specific applications. The exploration of alternative fluid

carriers, such as air and nitrogen, further adds to the versatility of this method, offering opportunities for tailored modifications to meet specific material requirements.

A summary of the bioactive compounds that have been impregnated into the polylactic acid matrix, highlighting the main changes, and the results achieved is described in Table 6.

Melt blending

Melt blending involves the direct mixing of bioactive compounds with polylactic acid during the melt processing stage. This process is typically performed using extruders or mixers, where the polylactic acid and the bioactive compound are heated and mixed together, using high operating temperatures, that exceed the melting point of the polymer, and/or high pressures. The resulting melt is then cooled and processed into the desired form: films, fibres, or moulded products (Fig. 5) (Tejada-Oliveros et al.

Table 6 Impregnation of bioactive compounds in polylactic acid

Bioactive compound	Methods	Changes on polylactic acid after treatment	Main results	References
<i>Biomedical applications</i>				
Extract from <i>Zataria multiflora</i> Boiss	Supercritical fluid-assisted impregnation with carbon dioxide	Decreased crystallinity and melting temperature Showed a homogeneous surface morphology	Exhibited antioxidant and antibacterial activities	Ardestani et al. (2022)
Ethanollic mango leaves extract	Supercritical fluid-assisted impregnation with carbon dioxide	Exhibited irregular surfaces	Improved antioxidant and anti-denaturant capacities	Rosales et al. (2021)
Olive leaf extract	Supercritical fluid-assisted impregnation with carbon dioxide	Small swelling of the filament after impregnation	The antioxidant capacity is influenced by the printing conditions	Verano-Naranjo et al. (2023)
Fluorine*	Supercritical fluid-assisted impregnation with air and nitrogen	Increased surface hydrophilicity	Improved biocompatibility, cell adhesion, and proliferation	Schroepfer et al. (2020)
<i>Packaging applications</i>				
Thymol and cinnamaldehyde	Supercritical fluid-assisted impregnation with carbon dioxide	Showed homogeneous dispersion Increased hydrophobicity and ductility Decreased Young's modulus value and thermal stability	Exhibited strong antibacterial activity. Potential in fruit packaging and as compostable films	Villegas et al. (2019)
Thymol and/or carvacrol	Supercritical fluid-assisted impregnation with carbon dioxide	Showed homogeneous distribution Improved, flexibility, extensibility, and ductility Decreased the tensile strength	Improved antioxidant activity	Lukic et al. (2020)
R-(–)-carvone	Supercritical fluid-assisted impregnation with carbon dioxide	Improved thermal, mechanical, and UV–Vis transmittance properties	Potential in food packaging	Miranda-Villa et al. (2022)

*Fluorine itself is not typically considered a bioactive compound. Although it is an element that when incorporated in materials can enhance bioactive properties

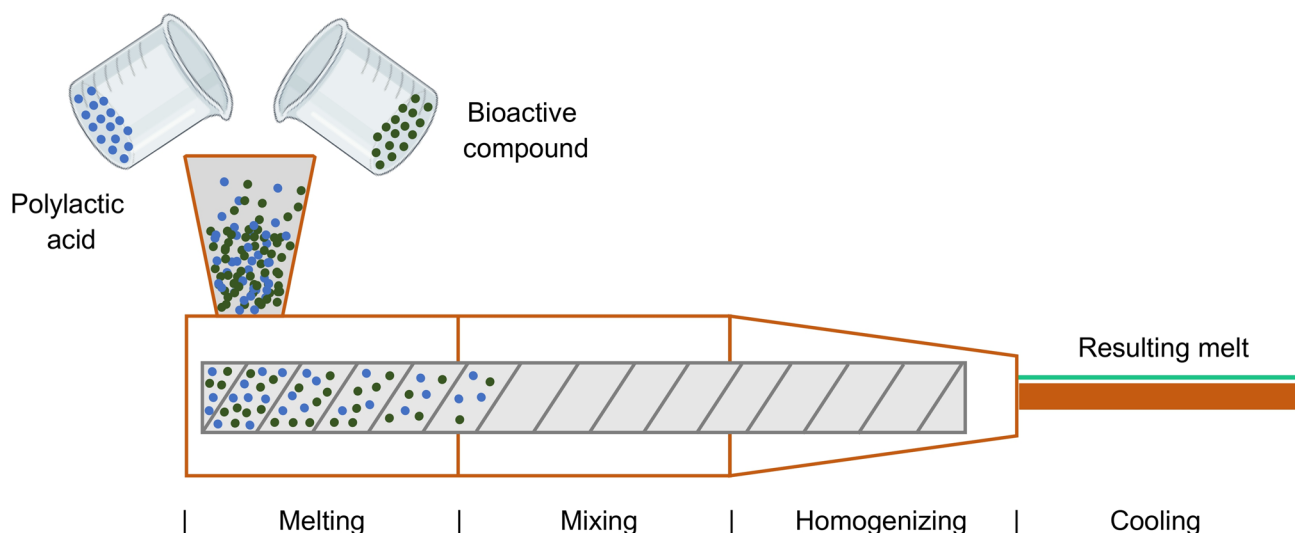


Fig. 5 The melt blending process

2022). Drawbacks of this process includes high energy consumption and temperatures, which can result in the thermal degradation of polylactic acid and the formation of lactic acid monomers (Lim et al. 2008).

Polylactic acid can be processed either on its own or in combination with other polymers. The addition of other polymers can modify the properties of polylactic acid to meet specific application requirements. One example is the study conducted by Suyatma et al. (2004), in which they blended polylactic acid with chitosan, a natural polymer that is biodegradable, biocompatible, edible, and nontoxic. The results showed an improvement in the water barrier properties and a decrease in the water sensitivity of the chitosan film.

Moreover, polylactic acid can also be processed with the incorporation of several organic and inorganic bioactive substances. These may include fillers, additives, reinforcements, nanoparticles, or natural materials, depending on the desired properties and intended use of the final product (de Kort et al. 2020).

In 2018, Darie-Niță et al. prepared polylactic acid-based blends through melt blending, incorporating different amounts of powdered ethanolic rosemary extract. The incorporation of the extract into polylactic acid improved elongation at break, rheological properties, and antibacterial and antioxidant activities. The polylactic acid/rosemary extract pellets possessed good *in vivo* biocompatibility, suggesting promising properties that could make them valuable for use as biomaterials in medical and biomedical devices (Darie-Niță et al. 2018).

A few years later, in 2021, Darie-Niță et al. encapsulated active agents, such as vitamin E and cold-pressed rosehip seed oil into chitosan. These agents, along with

bioplasticizers, were then mixed with polylactic acid. The resulting biocomposites exhibited enhanced processability, as well as improved physical–mechanical, thermal, water vapour barrier, antioxidant, and antimicrobial properties, demonstrating potential for applications in food packaging (Darie-Niță et al. 2021).

Recently, in 2023, Darie-Niță et al. incorporated sage, coconut oil, and montmorillonite nanoclay into polylactic acid using the melt blending process. By adjusting the type and quantity of these components, the authors aimed to control the structural, morphological, physicochemical, and biological properties of the resulting materials. Therefore, the researchers found that the prepared biocomposite exhibited the highest antioxidant and antimicrobial activities against *Staphylococcus aureus* and *Escherichia coli*, attributed to the synergistic interaction among the components (Darie-Niță et al. 2023).

Gavril et al. (2019) also used sage and lemon balm leaves to develop polylactic acid films. They evaluated the antioxidant capacity of these films revealing that the hydroxylation percentage of the lemon balm film was approximately $55.5 \pm 0.1\%$, while for the sage film was approximately $67.4 \pm 0.3\%$. This indicates that the presence of these bioactive compounds significantly enhanced the antioxidant activity of the films.

Applied to food packaging, Fu et al. (2023) prepared a film of polylactic acid incorporating curcumin. Curcumin was introduced as a chain extender in castor oil-based polyurethane, which was melt-blended with polylactic acid to create a sustainable ultraviolet shielding film. Curcumin contributed to the film's ultraviolet-shielding ability and antioxidant capacity. The results showed that the addition of castor oil-based polyurethane to the polylactic acid matrix

significantly enhanced the toughness and fracture characteristics of the films, while maintaining the thermal stability and low water swelling and solubility.

A different study developed by Freitas et al. (2023) incorporated extracts from rice straw (6 wt. %) into polylactic acid films through melt blending and compression moulding. The films prepared were characterised as to their structural and functional properties and assessed for their capacity to preserve fresh pork meat, as vacuum thermo-sealed bags, throughout 16 days of cold storage. The films exhibited negative changes in mechanical and barrier properties, however, enhanced oxygen barrier and ultraviolet-blocking abilities, effectively preserving fresh pork meat.

Regarding inorganic bioactive substances, Persson et al. (2014) incorporated hydroxyapatite particles into polylactic acid, using an extrusion process. The work focused on evaluating the surface structure of the composite and studying the effects of different hydroxyapatite densities on the initial attachment of murine calvarial preosteoblasts cells, in vitro. The enhanced cell behaviour and improved expression of key proteins indicated that the composites could support cell adhesion, suggesting their ability to contribute to bone regeneration and tissue growth.

In a different study, Backes et al. (2021) developed polylactic acid biocomposites by incorporating varying contents of β -tricalcium phosphate, through melt blending. The 3D printed screws produced using the polylactic acid/ β -tricalcium phosphate biocomposites exhibited excellent printability and accuracy. Furthermore, the materials exhibited favourable thermal, rheological, and mechanical properties, with potential to be used in the field of guided bone tissue engineering.

Even though melt blending has its downsides, studies demonstrate the effectiveness of this approach. The combination of polylactic acid with several organic and inorganic bioactive compounds can result in materials with improved mechanical, thermal, and biological properties, opening avenues for sustainable and functional materials in different industries.

A summary of the bioactive compounds that have been incorporated into the polylactic acid matrix by melt blending, highlighting the main changes, and the results achieved is described in Table 7.

Solvent casting

The method of solvent casting involves dissolving the bioactive compound in a compatible solvent and then mixing it with polylactic acid, to ensure uniform dispersion. The mixture is then cast into a mould or onto a substrate. The solvent is evaporated or removed, leaving behind a solid polylactic acid composite with the bioactive compound embedded within (Fig. 6).

The solvent casting technique has been noted for its superior outcomes in the development of biocomposites compared to melt blending method, especially due to the improved dispersion of the compounds and the possibility of hydrogen bonding with the polymer matrix (Qasim et al. 2021). This process is simple and results in the formation of polylactic acid material that is non-porous or has minimal porosity. However, it has drawbacks, such as time and energy consumption, limited scalability to laboratory settings (Lukic et al. 2020; Qasim et al. 2021).

Mukaffa et al. (2022) synthesized biocomposites using polylactic acid filled with piper betle fibre, known for their medicinal properties. Alkali-treated piper betle fibre significantly enhanced the biocomposite's tensile properties compared to the untreated, but elongation at break decreased. Scanning electron microscopy confirmed strong bonds between treated piper betle fibre and polylactic acid, reducing cavities, making these materials suitable for potential use in various applications.

In the biomedical field, Cai et al. (2002) modified polylactic acid surfaces by entrapping poly(aspartic acid), using the solvent casting process. Water contact measurement of the film showed a change of the surface hydrophilicity, resulting in a positive effect on cell adhesion, proliferation, and differentiation, enhancing their cell affinity.

Another important field is the packaging applications. In this area, Jamshidian et al. (2013) prepared polylactic acid films with natural and synthetic antioxidants: ascorbyl palmitate, α -tocopherol, butylated hydroxyanisole, butylated hydroxytoluene, propyl gallate, and *tert*-butylhydroquinone. Films were exposed to various ethanol concentrations at 40 °C and 20 °C for 60 days, and the release of antioxidants was measured. The obtained diffusion and partition coefficients can be used to develop polylactic acid antioxidant-active packaging for controlling oxidation reactions in diverse food products, while reducing the need for directly added antioxidants, ensuring food safety and quality.

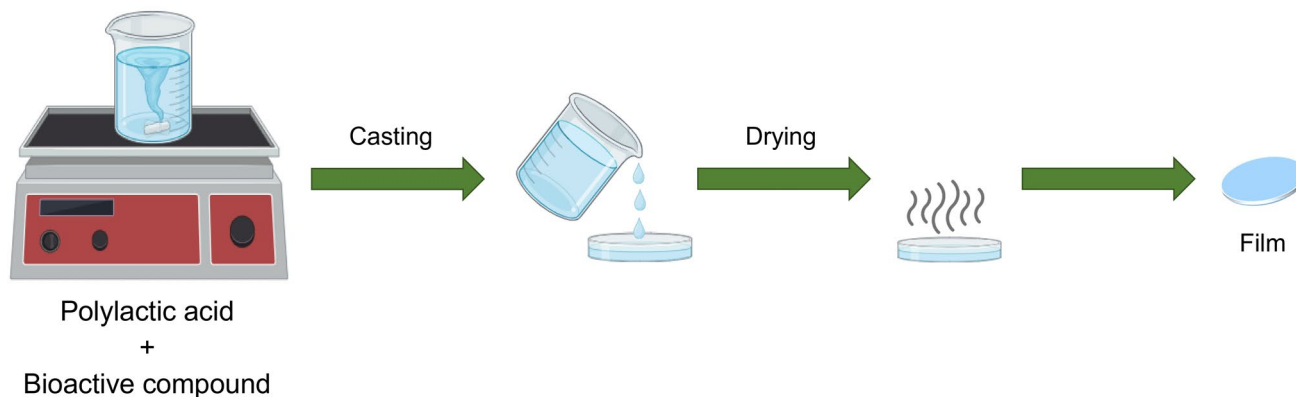
Also applying natural antioxidants, Stoll et al. (2019) improved the light and oxygen barrier properties of polylactic acid films by incorporating carotenoid extracts (β -carotene, lycopene, and bixin). The films demonstrated antioxidant and light barrier properties in preserving sunflower oil, with bixin showing the best performance. This study highlights the potential of carotenoid-based polylactic acid films for antioxidant active packaging in food preservation.

Salmieri et al. (2014) developed bioactive films composed of supramolecular polylactic acid and cellulose nanocrystals by incorporating oregano essential oil as an antimicrobial agent. The resulting films exhibited strong antimicrobial activity, inhibiting the growth of *Listeria monocytogenes*. These films, applied as food packaging, maintained their properties and released bioactive

Table 7 Melt blending of bioactive compounds in polylactic acid

Bioactive compound	Method	Changes on polylactic acid after treatment	Main results	References
<i>Biomedical applications</i>				
Sage and coconut oil	Melt blending processing	Polylactic acid/Sage increased hydrophilicity, while coconut oil significantly increased hydrophobicity Addition of sage decreased the tensile strength and Young's modulus	Enhanced antioxidant and antimicrobial activities	Darie-Niță et al. (2023)
Hydroxyapatite	Extrusion process	Surface roughness increased with the concentration of hydroxyapatite loading	Enhanced cell behaviour and adhesion Potential to bone regeneration and tissue growth	Persson et al. (2014)
β -Tricalcium phosphate*	Melt blending process	Improved thermal and rheological properties	Improved cell viability Potential in the field of bone tissue engineering	Backes et al. (2021)
<i>Packaging applications</i>				
Ethanollic rosemary extract	Melt blending process	Improved elongation at break and rheological properties Improved thermoxidative stability	Improved both antibacterial and antioxidant activities, biocompatibility, and blood parameters	Darie-Niță et al. (2018)
Vitamin E and rosehip seed oil	Encapsulation, melt blending process	Enhanced processability, physical–mechanical properties, thermoxidative stability and water vapour barrier	Enhanced antioxidant, and antimicrobial properties	Darie-Niță et al. (2021)
Sage and lemon balm leaves	Melt blending process	Decreased migration of certain polylactic acid oligomers, and the thermal stability	Enhanced the antioxidant activity	Gavril et al. (2019)
Curcumin	Melt blending process	Improved thermal stability, low water swelling, and solubility	Enhanced antioxidant activity and UV blocking abilities	Fu et al. (2023)
Extracts from rice straw	Melt blending process	Improved mechanical properties	Enhanced antioxidant, and antimicrobial properties, oxygen barrier and UV blocking abilities	Freitas et al. (2023)

*While β -tricalcium phosphate itself is not a bioactive compound in the traditional sense, it is considered a bioactive material

**Fig. 6** The solvent casting method

compounds during storage, showing their potential for preserving the quality and safety of vegetable products.

In a different study, Roy and Rhim (2020) prepared functional films based on polylactic acid and curcumin using the solvent casting method. The composite film showed improved mechanical and antioxidant properties, thermal stability, and some antibacterial activity, having the potential to extend shelf life and ensure the safety of food products.

Using propolis as bioactive agent, Ulloa et al. (2019) developed active films by incorporating various concentrations of propolis into polylactic acid. The addition of propolis into the polylactic acid matrix had an impact on its thermal properties, particularly the glass transition temperature. These films also exhibited antioxidant and antimicrobial properties, making them suitable for food packaging. Additionally, biodegradation assays demonstrated their potential as environmentally friendly materials.

A similar study with different concentrations of propolis extract was conducted by Safaei and Roosta Azad (2020). The presence of propolis extract negatively affected the tensile strength, elongation at break, and elastic modulus of the polylactic acid films. However, when polyethylene glycol/calcium carbonate was added to the films, it was verified that it improved both mechanics and antimicrobial effects. This enhancement makes the material suitable for packaging, with the potential to extend the shelf life of meat products.

Regarding inorganic bioactive compounds, Martínez-Abad et al. (2013) incorporated silver ions onto polylactic acid films using the solvent casting technique, resulting in 1%-silver- polylactic acid films. These films demonstrated dose-dependent antiviral and antibacterial activity on food samples. The ability of these films to eliminate viral infectivity show their potential as effective tools for reducing viral contamination, enhancing food safety.

Another inorganic compound used is zinc oxide, this compound has been recognized for its antimicrobial properties and has been widely employed for controlling bacterial growth in various applications. Its use as an antimicrobial agent has been approved by the Food and Drug Administration, indicating that it is considered safe for use in different contexts (Esmailzadeh et al. 2016).

Li and coworkers (2017) synthesized a novel nanopackaging film by incorporating zinc oxide nanoparticles into a polylactic acid matrix. A nano-blend film was prepared by incorporating 6% cinnamaldehyde into a blend of polylactic acid and zinc oxide nanoparticles. Its effect on the shelf-life quality of fresh-cut apple was studied at 4 ± 1 °C for 14 days. The results revealed that the film maintained the firmness, total phenolic content, colour, and sensory quality of the fresh-cut apples and exhibited remarkable inhibition of microbial growth.

Also using zinc oxide, Kim et al. (2019) prepared a series of polylactic acid/zinc oxide bionanocomposite films, using the solvent casting method. These films exhibited zinc oxide content-dependent physical properties and antibacterial activities. They displayed decreased thermal stability and barrier properties, but increased hydrophobicity, antibacterial activity, and ultraviolet light barrier, allowing them to have potential as food packaging materials.

Solvent casting arises as a versatile method for incorporating bioactive compounds into polylactic acid, offering a simple process to create materials with enhanced functionalities for diverse applications.

A summary of the bioactive compounds that have been incorporated into the polylactic acid matrix by solvent casting, highlighting the main changes and the results achieved is described in Table 8.

Electrospinning

Electrospinning is a technique used to produce nanofibres with high surface area, small inter-fibrous pore size, and high porosity. Basically, in this method, a solution containing polylactic acid and the bioactive compound is electrostatically spun into fine fibres (Fig. 7) (Echeverría et al. 2019; Duygulu et al. 2020).

Despite the advantages of the electrospun fibres, such as high surface area, easy surface modification, and the ability to functionalize polymeric chains at a low cost, the productivity constraints of electrospinning limit its suitability for large-scale industrial applications (Mishra et al. 2019).

Electrospun polylactic acid fibres have been investigated and used as potential biomedical devices. Zhou et al. (2011) developed polylactic acid/carbonated calcium deficient hydroxyapatite bionanocomposite fibres, via electrospinning. The incorporation of the bionanocomposite into the polylactic acid scaffold resulted in a decreased in fibre diameters, which enhanced the material's mechanical properties. Moreover, it also contributed to the improved bioactivity and biocompatibility of the scaffold, promoting the attachment and adhesion of cells.

Wu et al. (2018) prepared bioactive polylactic acid nanofibrous scaffolds by incorporating nan graphene oxide dots during the electrospinning process. The scaffolds exhibited enhanced mechanical properties, hydrophilicity, good cytocompatibility, and osteo-bioactivity with potential for bone tissue engineering applications.

On the other hand, Yu et al. (2018) developed a bioactive resveratrol-polylactic acid-gelatine porous nano-scaffold, using the same method, freeze drying, and uniform dispersion techniques. This experimental approach demonstrated improved cartilage repair.

Samadian et al. (2020) similarly prepared a functional scaffold by combining 3D polylactic acid/polycaprolactone

Table 8 Solvent casting of bioactive compounds in poly(lactic acid)

Bioactive compound	Method	Changes on poly(lactic acid) after treatment	Main results	References
Piper beetle fibre	Solvent casting	The addition of the fibre content improved tensile strength, elastic modulus, and increased surface roughness	Potential applications of these materials for several purposes	Mukaffa et al. (2022)
<i>Biomedical applications</i>				
Poly(aspartic acid)*	Solvent casting	Increased surface hydrophilicity	Enhanced osteoblast proliferation	Cai et al. (2002)
<i>Packaging applications</i>				
Ascorbyl palmitate and α -tocopherol	Solvent casting	Films with $100 \pm 5 \mu\text{m}$ of thickness	Potential for antioxidant-active packaging	Jamshidian et al. (2013)
Carotenoid extracts	Solvent casting	Films with $125 \pm 5 \mu\text{m}$ of thickness	Improved both antioxidant and antibacterial activity, and light barrier properties	Stoll et al. (2019)
Oregano essential oil	Solvent casting	Increased elasticity, fracture strain, and maintained water vapour permeability	Exhibited strong antimicrobial activity and slow release of total phenolic compounds	Salmieri et al. (2014)
Curcumin	Solvent casting	Improved physical–mechanical, thermal stability, and water vapour barrier properties	Improved antioxidant and antimicrobial properties and UV barrier properties	Roy and Rhim (2020)
Propolis	Solvent casting	Increased thickness Decreased elastic modulus, tensile strength, and water vapour permeability	Exhibited both antioxidant and antimicrobial properties Potential as environmentally friendly materials	Ulloa et al. (2019)
Propolis extract	Solvent casting	Improved flexibility, and stiffness	Enhanced antioxidant and antimicrobial properties	Safaei and Roosta Azad (2020)
Silver	Solvent casting	Poly(lactic acid) films containing 1% silver had a thickness ranging from approximately 30 to 40 μm	Demonstrated strong antibacterial and antiviral activities	Martínez-Abad et al. (2013)
Zinc oxide	Solvent casting	Decrease thermal stability and barrier properties Improved hydrophobicity	Excellent UV protection and antibacterial properties	Kim et al. (2019)
Zinc oxide and cinnamaldehyde	Solvent casting	Improved surfaces roughness, water vapour permeability and elongation at break Decreased tensile strength and elastic modulus	Maintained total phenolic content, and exhibited inhibition of microbial growth	Li et al. (2017)

*Poly(aspartic acid) is a biodegradable and biocompatible polymer. Since it exhibits several beneficial biological properties, can be considered an active compound

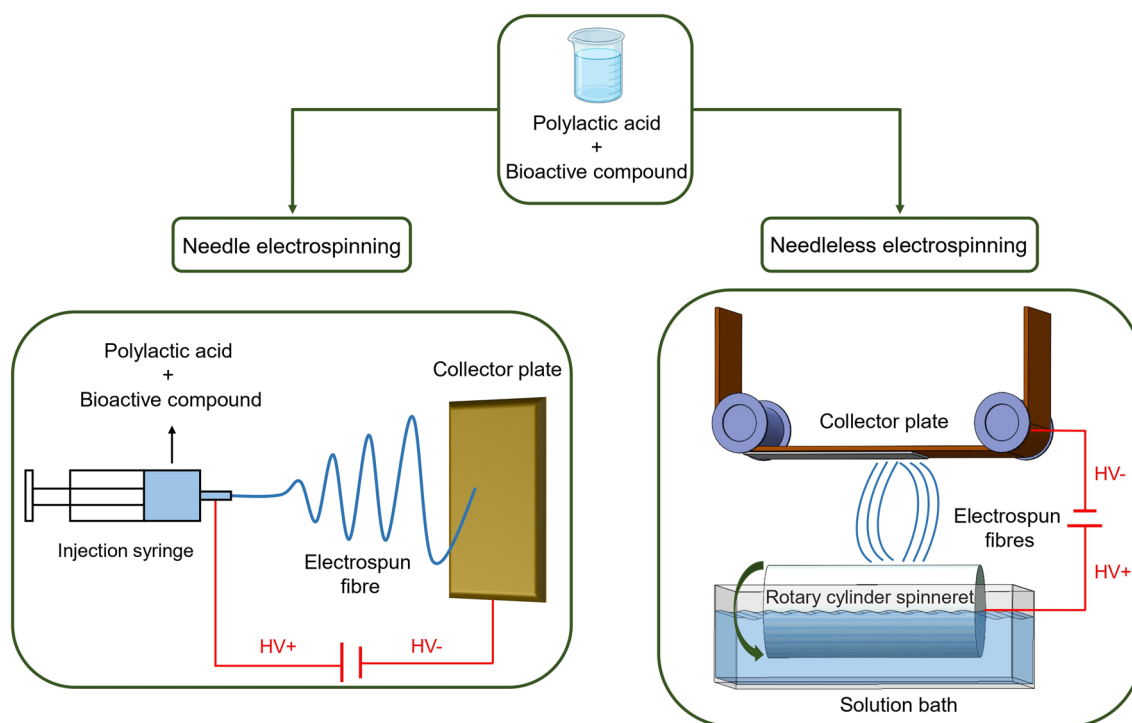


Fig. 7 The electrospinning method

with gelatine nanofibres and taurine. The gelatine nanofibres were electrospun and incorporated into a polymer solution with varying taurine concentrations. Afterwards, the solution was transformed into a 3D porous scaffold using thermally-induced phase separation. The scaffolds demonstrated biocompatibility, supported cell viability, and in vivo showed new bone formation in treated defects.

More recently, Imani et al. (2021) developed a neural tissue engineering scaffold by incorporating polypyrrole-grafted gelatine into electrospun poly(lactic acid) nanofibres. When testing the samples for supporting nerve cell adhesion and growth, scaffolds with 15 and 20% polypyrrole showed the best results, indicating their potential in nerve regeneration and tissue engineering applications.

With similar results, Canales et al. (2022) investigated the incorporation of bioactive glass and magnesium oxide nanoparticles into electrospun poly(lactic acid) fibres. The addition of both nanoparticles synergistically enhanced the bioactivity and antimicrobial properties of poly(lactic acid). All bioactive glass composites exhibited bioactivity through hydroxyapatite precipitation. Although magnesium oxide nanoparticles didn't add bioactivity, it exhibited antimicrobial characteristics by reducing *Staphylococcus aureus* viability.

In a different study, Stoyanova et al. (2014) used electrospinning to produce poly(lactic acid)/polybutylene succinate

materials. These materials exhibited thermomechanical properties influenced by the fibre alignment and polybutylene succinate content. As this content increased, the material transitioned from being plastic to brittle. It also demonstrated antibacterial properties when loaded with antibacterial agents, making them potential candidates for antibacterial fibrous materials.

Regarding packaging applications, Quiles-Carrillo et al. (2019) developed bi- and multilayer poly(lactic acid) films incorporating 40 wt. % of gallic acid via electrospinning. Bilayer films exhibited quick gallic acid release, suitable for short-life cycle packaging, while multilayer films showed a sustained release for over 1000 h, ideal for longer shelf life. All films demonstrated enhanced thermal stability, delaying poly(lactic acid) degradation by 10 °C.

In conclusion, electrospinning stands out as a powerful technique for producing bioactive poly(lactic acid), demonstrating their potential in enhancing mechanical properties, promoting bioactivity, and enabling controlled release of bioactive compounds, thus opening avenues for advancements in tissue engineering, drug delivery, and sustainable food packaging.

A summary of the bioactive compounds that have been incorporated into the poly(lactic acid) matrix by electrospinning, highlighting the main changes, and the results achieved is described in Table 9.

Table 9 Electrospinning of bioactive compounds in polylactic acid

Bioactive compound	Method	Changes on polylactic acid after treatment	Main results	References
<i>Biomedical applications</i>				
Hydroxyapatite	Electrospinning	Decreased the diameter of the fibres Improved mechanical properties, bioactivity and biocompatibility	Improved bioactivity and enhanced biocompatibility particularly in cell adhesion	Zhou et al. (2011)
Nan graphene oxide dots	Electrospinning	Enhanced mechanical properties, hydrophilicity and cytocompatibility	Cytocompatibility and osteo-bioactivity. Potential for bone tissue engineering	Wu et al. (2018)
Resveratrol and gelatin	Electrospinning	The nano-scaffold showed finer fibre diameter, larger surface area, higher porosity, and stable drug release	Demonstrated improved cartilage repair	Yu et al. (2018)
Gelatine and taurine	Electrospinning and thermally-induced phase separation technique	Increased porosity, and wettability Decreased the compressive strength	Showed biocompatibility, cell viability, and bone formation in treated defects	Samadian et al. (2020)
Gelatin	Electrospinning	Improved conductivity and surface hydrophilicity	Showed conditions for nerve cell adhesion and growth	Imani et al. (2021)
Bioactive glass	Electrospinning	The scaffold showed changes in Young's modulus Increased fibre diameter and enhanced the bioactivity	Exhibited antimicrobial characteristics, and a good osteoblastic phenotype expression capacity	Canales et al. (2022)
Polybutylene succinate*	Electrospinning, freeze drying, and uniform dispersion techniques	Increased crystallinity, Young's modulus, and tensile strength	Exhibited antibacterial properties Repaired cartilage injuries	Stoyanova et al. (2014)
<i>Packaging applications</i>				
Gallic acid	Extrusion and electrospinning	Homogenous fibres with rough surface Improved thermal stability and conductivity	Exhibited antioxidant activity and sustained release over an extended period	Quiles-Carrillo et al. (2019)

*Polybutylene succinate is a biodegradable and biocompatible polymer, however in combination with polylactic acid acquire biologically active properties

In situ polymerization

In the in situ polymerization method, the bioactive compound is chemically incorporated into the polylactic acid matrix, during the polymerization process. It can be modified or functionalized to react with the monomers of polylactic acid. This process offers good control over the distribution and stability of the bioactive compound within the matrix.

The in situ polymerization method can be used in the development of carriers in drug delivery, as demonstrated in the study conducted by Tudorachi et al. (2013). In their work, they detailed the synthesis and characterization of polylactic acid-co-aspartic acid copolymers, serving as biodegradable carriers for drug delivery systems. The presence

of aspartic acid improved thermal stability compared to pure polylactic acid. Additionally, loading diclofenac sodium into the copolymers revealed, in vitro, release dependency on initial molar ratios and particle size, indicating their potential for controlled drug delivery systems.

Working for the same objective, Danafar et al. (2017) developed a bioactive polylactic acid through a reaction between polylactic acid-polyethylene glycol-polylactic acid and lisinopril, using dicyclohexylcarbodiimide and dimethylaminopyridine as catalysts. The lisinopril-conjugated with the copolymers exhibited pH-dependent and sustained release profiles.

On the same subject Ding et al. (2018) synthesized a star-shaped poly(L-lactide), through ring opening polymerization of L-lactide. Afterwards, bovine serum albumin

was loaded into star-shaped poly(L-lactide) microspheres, using a double-emulsion solvent evaporation method. The results showed that the bovine serum albumin-loaded microspheres displayed a gradual release in phosphate buffer saline, indicating the potential for drug delivery applications.

Regarding the incorporation of inorganic compounds, Hazarika et al. (2022) prepared a nanohybrid material by incorporating a crystalline form of titanium oxide into silk nanocrystals, by sol–gel method. This nanohybrid was used as a co-initiator for in situ polymerization of polylactic acid, resulting in a nanocomposite with favourable properties, such as high molecular weight, processibility, and hydrophobicity, making it a promising candidate for smart textile technology.

In situ polymerization emerges as a flexible method for incorporating bioactive compounds into polylactic acid, offering precise control over distribution and stability within the matrix.

A summary of the bioactive compounds that have been incorporated into the polylactic acid matrix through in situ polymerization, highlighting the main changes, and the results achieved is described in Table 10.

Perspective

The incorporation of bioactive compounds in polylactic acid offers favourable mechanical and thermal properties, making them viable alternatives to non-biodegradable

petroleum-based products. These properties depend on factors, such as production processes, bioactive compounds, reinforcement content, chemical treatments, and interfacial bonding. The materials show potential for high-performance applications in several industries, including domestic appliances, textiles, biomedical devices, and food packaging.

Regarding medical applications, polylactic acid is used in the production of several biomedical devices. Its biodegradability and compatibility with the human body make them suitable for drug delivery systems, which represent an emerging area for polylactic acid materials. However, achieving performance comparable to conventional processes remains a challenge in 3D printing applications.

In order to ensure the optimal performance of bioactive polylactic acid materials, it is crucial to maintain their efficiency over the required timeframe, while ensuring degradation occurs as intended. Therefore, it is crucial to evaluate these applications in real systems and consider the interactions with the external environment.

Future research should focus on developing structured architecture network frameworks to improve the microstructural homogeneity and physicochemical performance of bioactive polylactic acid materials. Since, these materials are already being used in various applications, more research and development efforts are needed to reduce processing costs, improve performance, and increase utilization in industrial settings.

Table 10 In situ polymerization of bioactive compounds in polylactic acid

Bioactive compound	Method	Changes on polylactic acid	Main results	References
<i>Biomedical applications</i>				
Aspartic acid	In situ polymerization, precipitation and solvent evaporation method	Smaller particles in copolymer/drug systems compared to copolymer Low polydispersity index Increased thermal stability	Improved diclofenac sodium/copolymers release Potential for drug delivery systems	Tudorachi et al. (2013)
Lisinopril*	In situ polymerization	Molar weight of 10 kD and a polydispersity index of 1.27	Exhibited pH-dependent and sustained release profiles	Danafar et al. (2017)
Xylitol	In situ polymerization, double-emulsion solvent evaporation method	Increased the molar weight and the polydispersity index. The microspheres bovine serum albumin/polymer showed an increase in diameter, a smoother surface and enhanced drug encapsulation efficiency	Exhibited slow-release behaviour in phosphate buffer Potential for drug delivery applications	Ding et al. (2018)
<i>Textile applications</i>				
Titanium oxide	The sol–gel method, in situ polymerization, and electrospinning	Increased crystallinity, thermal stability, and hydrophobicity	Enhancement of the material's self-cleaning	Hazarika et al. (2022)

*Lisinopril is a pharmaceutical active drug

Conclusion

Poly(lactic acid) is recognized as a versatile polymer with remarkable physical and biological properties. It has high interest for bioeconomy as a substitute of fossil-based plastic materials with less impact for the environment. On the other hand, selecting raw materials that do not compete with food and feed, along with mindful land use, is crucial for a sustainable advanced materials production and a biobased society. This work provides a comprehensive overview of current research methods employed in the production of bioactive poly(lactic acid) materials, namely, the surface modification techniques and the incorporation of bioactive molecules into poly(lactic acid) matrices. It discusses the preparation of these materials through several processing methods, with a particular emphasis on understanding the influence of processing variables on shaping material properties. It also assesses the performance of these materials and explores their possible applications in different fields. The selection of the appropriate processing methods and parameters is crucial, considering the desired properties of the final product.

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Declarations

Conflict of interest The authors declare no competing financial interest.

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