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POLYGLUTAMIC ACID: AN INNOVATIVE AND MULTIFUNCTIONAL BIOPOLYMER

BY

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Abstract. Polyglutamic acid (γ-PGA) is a biodegradable and environmentally friendly microbial biopolymer known for its biocompatibility, biodegradability and versatility. This paper reviews the structure, production methods and main applications of γ-PGA in agriculture, medicine, wastewater treatment, food technology and cosmetics. In agriculture, γ-PGA can improve soil fertility, increase fertilizer efficiency and contribute to the remediation of saline soils. In the medical field, it has been investigated for drug delivery systems, tissue adhesives and bone regeneration materials. Its adsorption and flocculation properties make it useful for wastewater treatment and other environmental applications. In addition, γ-PGA is used in the food and cosmetics industries due to its cryoprotective and moisturizing effects. Despite its broad range of applications, the large-scale use of γ-PGA is still limited by high production costs and relatively low biosynthetic yields. Further advances in production technologies may contribute to the wider implementation of this biopolymer in industrial and biomedical fields.

Keywords: biosynthesis, biodegradation, biomedical applications, environmental protection, sustainability.

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1. Introduction

In recent years, microbial biopolymers have attracted considerable interest as sustainable alternatives to conventional synthetic polymers. Among them, polyglutamic acid (γ-PGA) stands out due to its biodegradability, low toxicity and compatibility with biological systems. The increasing demand for biodegradable materials is driven by environmental concerns, stricter regulations regarding plastic waste and the transition towards a circular bioeconomy (Nanda *et al*., 2022). Consequently, bio-based polymers have attracted growing attention in both research and industry as sustainable alternatives to petroleum-derived materials. Among these materials, microbial biopolymers such as γ-PGA have gained increasing interest because of their biodegradability, biocompatibility and the possibility of being produced through microbial fermentation (Elbanna *et al*., 2024).

Polyglutamic acid (PGA) was first discovered in 1937 by Ivanovici and his collaborators in Bacillus anthracis (Elbanna *et al*., 2024). γ-PGA has also been identified as the main component of the sticky and viscous mucilage in Natto, a traditional Japanese food with health benefits. Natto has been used commercially and domestically for over a thousand years and is produced by steam-treating small soybeans and fermenting them with a culture of *Bacillus subtilis* (natto) (Najar and Das, 2015).

Although several review papers have discussed γ-PGA, they often focus on specific aspects such as microbial production, biosynthesis or selected biomedical applications. More recent studies have also highlighted the growing interest in γ-PGA for agriculture, environmental protection, food technology and regenerative medicine. An updated overview that integrates these recent developments can provide a broader perspective on the current state of γ-PGA research and its future industrial and biomedical potential (Li *et al*., 2022; Al-wahili *et al*., 2023; Elbanna *et al*., 2024). Currently, γ-PGA is produced by Bacillus species, but low yields and high costs limit its industrial use. The solution to these difficulties may lie in genetic manipulation, optimization of the culture medium and identification of more efficient microbial producers (Elbanna *et al*., 2024).

The aim of this review is to provide an updated overview of γ-PGA by presenting its structure, biosynthesis and the main application areas reported in the recent literature. In addition, the review discusses the current limitations associated with γ-PGA production and highlights future research directions that may support its wider industrial and biomedical use.

2. Methodology

This review was prepared based on a literature survey of scientific publications related to γ-polyglutamic acid (γ-PGA). The literature search was performed using major scientific databases and academic search engines, including Scopus, Web of Science, ScienceDirect, PubMed and Google Scholar. Reference management and organization of the selected publications were carried out using Mendeley.

Priority was given to peer-reviewed articles published in English, with particular emphasis on recent studies addressing the structure, biosynthesis, properties and applications of γ-PGA. Earlier publications were also included when they represented fundamental contributions or were frequently cited in the field. When several publications addressed similar topics, preference was given to the most recent review articles and original research papers reporting representative experimental results.

The selected literature was analysed and organized according to the main research areas of γ-PGA, including agriculture, environmental protection, medicine, food technology and cosmetics, in order to provide an updated overview of its current applications, limitations and future perspectives.

3. γ-PGA structure

Poly-γ-glutamic acid (γ-PGA) is a homopolyamide formed from D- and L-glutamic acid monomers, linked by amide bonds between the α-amino and γ-carboxyl groups. This unique structure confers γ-PGA resistance to proteases and qualifies it as an optically active biopolymer with a chiral centre in each glutamate unit. γ-PGA can be synthesized by many microorganisms and is available in three main forms: D-PGA, L-PGA and D, L-PGA. These forms, collectively called γ-PGA, exhibit structural and functional variations that influence its applications. An important characteristic of γ-PGA is its behavior in aqueous media. The polymer is readily soluble when present as sodium, potassium, and ammonium or divalent metal salts, whereas the protonated form exhibits poor water solubility. Complete biodegradability and non-toxicity to humans make γ-PGA a versatile material for industrial and biomedical uses (Najar and Das, 2015).

The molecular weight of γ-PGA varies between 100 KDa and 2500 KDa and is determined by fermentation time, pH, degree of aeration and the way agitation is performed. Increasing fermentation time may reduce the molecular weight due to enzyme activity catalysing the hydrolytic decomposition of the polymer (Najar and Das, 2015).

The conformation of γ-PGA is influenced by concentration and pH. At low concentrations (0.1% w/v) and pH below 7, γ-PGA adopts an α-helix conformation, stabilized by intramolecular hydrogen bonds. At pH above 7, the β-sheet conformation predominates, which maximizes the exposure of negative

charges. This conformational change is related to the tendency of deprotonation of carboxyl groups at low proton (H^+) concentrations. Recently, circular dichroism studies have also indicated the presence of disordered conformations, although the mechanisms remain poorly elucidated (Najar and Das, 2015).

4. Production of γ-PGA

The production of γ-PGA is a biosynthesis process mainly carried out by microorganisms such as Bacillus subtilis, Bacillus licheniformis and other species of the genus Bacillus. Microorganisms use glucose, glycerol, or peptone as sources of carbon and nitrogen, with their ratio being adjusted to maximize biopolymer production. The fermentation time varies between 24 - 72 h, and the fermentation conditions are as follows: optimal pH is between 6 - 8, fermentation temperature is between 30 - 37°C, aeration rate of 1 L air L^{-1} medium min^{-1} and optimal agitation for uniform dispersion of nutrients in the bioreactor (Bajaj and Singhal, 2011b).

To optimize the biosynthesis process of the biopolymer, various techniques can be used such as strain identification or genetic modification of strains to increase the production yield, the use of alternative sources of carbon and nitrogen, for example from agricultural waste, which would minimize costs, and the implementation of new semi-continuous or continuous technologies that would increase the yield while reducing process times (Bajaj and Singhal, 2011b).

Table 1 presents a comparison of γ-PGA with representative biodegradable biopolymers, highlighting their main characteristics, advantages, limitations and representative applications.

Table 1
Comparison of γ-PGA and representative biodegradable biopolymers

Biopolymer	Origin	Chemical nature	Main advantages	Main limitations	Representative applications	Key review references
γ-Polyglutamic acid (γ-PGA)	Microbial (*Bacillus* spp.)	Polyamide	Biodegradable, biocompatible, high water-retention capacity, easily functionalized	High production cost; low biosynthetic yield; downstream processing challenges	Drug delivery, tissue engineering, wastewater treatment, agriculture, food preservation, cosmetics	Bajaj and Singhal (2011b); Najar and Das (2015); Elbanna *et al.* (2024)
Chitosan	Chitin from crusta-ceans or fungi	Polysaccha-ride	Biocompatible, bioadhesive, antimicrobial, film-forming	Limited solubility at neutral and alkaline pH	Drug delivery, wound healing tissue engineering, antimicrobial coatings	Kim *et al.* (2023)
Alginate	Brown algae or bacterial fermenta-tion	Polysaccha-ride	Biocompatible, mild gelation conditions, hydrogel-forming ability	Low mechanical strength and limited cell adhesion	Cell encapsulation, wound dressings, drug delivery, tissue engineering	Abka-khajouei *et al.* (2022)
Hyaluronic acid	Animal tissues or microbial fermenta-tion	Glycosami-noglycan	Excellent biocompatibility, high water-binding capacity, promotes tissue regeneration	Rapid enzymatic degradation, relatively high production cost	Dermal fillers, ophthalmology, tissue engineering, wound healing	Yasin *et al.* (2022)
Polyhydroxy alkanoates (PHA)	Microbial fermenta-tion	Polyester	Biodegradable, good mechanical properties, suitable for long-term biomedical applications	High production cost and limited processability	Sustainable packaging, sutures, implants, tissue engineering	Tan *et al.* (2021)

5. Applications

5.1. Agriculture

Due to its biodegradability and non-toxic properties, γ-PGA can be used in agricultural applications. Nanoparticles of γ-PGA/Chitosan are used to encapsulate gibberellic acid (GA3), which is a hormone used as a plant growth regulator. Using nanoparticles to deliver GA3 has the advantage of protecting the hormone from degradation and keeping it longer on the plant surface, which can help to minimize the concentration applied at treatment (Pereira *et al*., 2017).

γ-PGA can also be used in the phytoremediation of saline soils. Due to its structure, specifically the γ -COOH group, it can form chelate complexes with various ions. This property is the basis of the desalination application, which consists in retaining Ca^{2+}, Mg^{2+} and NO_3^-, as well as removing heavy metal ions from the soil. It has been shown that at an optimum concentration of 1000 mgL^{-1} γ-PGA, 93.25% Ca^{2+}, 94.78% Mg^{2+} and 84.26% NO_3^- are retained. An important role in this is the biodegradability of the polymer. As the polymer degrades over time, it releases the retained ions. This application represents a potential remediation method for polluted soils (Mu *et al*., 2021).

To promote the growth of maize crops on soils affected by excessive salinization, γ-PGA can also be combined with plant growth promoting bacteria (PGPR). Following the combined application of γ-PGA and PGPR there were a number of positive effects such as: significant increases in plant height, leaf area and plant weight. It also prevented Na^+ accumulation in leaves and roots under salt stress. The combined application is more valuable for plant growth than treating with PGPR alone. There are currently no studies that would explain how PGA can support PGPR, but the results of the study may provide valuable material for future research in this area (Zeng *et al*., 2024).

Guo *et al* demonstrated that γ-PGA had positive effects on the growth of alfalfa on sandy soils, greatly improving soil physical and chemical properties and stimulating plant growth. Treatment with γ-PGA also had a positive impact on the rhizosphere microbial community, increasing its diversity and uniformity (Guo *et al*., 2024).

γ-PGA can also be used to increase fertilizer use efficiency. Reducing the concentration of fertilizers containing nitrogen, phosphorus and potassium, but adding γ-PGA can compensate for fertilizer deficiency while increasing the productivity of cultivated vegetables and increasing the diversity, abundance and uniformity of soil bacteria (Bai *et al*., 2020).

γ-PGA has also been compared with Bacillus subtilis cells as a biostimulant for rice growth and soil quality improvement. It was shown that even at lower concentrations γ-PGA exhibits superior effects on plant growth compared to B. subtilis, significantly enhancing plant growth parameters and soil physical characteristics. However, the price of obtaining γ-PGA is still high and its large-scale agricultural application remains economically limited. Future studies focused on obtaining γ-PGA through the fermentation of food waste may represent a promising approach to reducing the production cost of the polymer (Ngearnpat *et al*., 2023).

5.2. Wastewater remediation

Due to its structure and functional groups, γ-PGA has demonstrated excellent properties in the adsorption of heavy metal ions. This property underpins the remediation of the environment and especially contaminated

waters. The free acidic form of γ-PGA exhibits limited water solubility, whereas its salt forms are highly water-soluble. PGA/gelatine and PGA/Fe_3O_4 were used for adsorption of Cu^{2+}, Pb^{2+}, and Cd^{2+} ions. The optimum pH values for adsorption were 4.6 and 6, and the temperature was 15 - 20°C, the adsorption capacity being 1158 mg/g, 1129 mg/g and 301 mg/g respectively (Mu *et al*., 2018). Hg^{2+} ions can be adsorbed by γ -PGA at the optimum values of pH=6 and T=30°C, with an adsorption capacity of 96.79 mg/g (Inbaraj *et al*., 2009).

γ-PGA can also be used to create specific sensors to detect contaminants such as Bisphenol A, which has multiple negative effects. The sensor containing a composite of γ-PGA and amino-functionalized carbon nanotubes (AF-CNTs) can rapidly detect contaminants, representing an important method in water quality control. The sensor is fabricated by depositing the nanocomposite using the layering method. AF-CNT is used to increase the electron transfer surface area and increase the sensitivity of the sensor, and γ-PGA contributes to efficient immobilization of molecules on the sensor surface. The experimental results demonstrated high sensitivity, increased stability and a detection limit of a few nanomoles, which is superior to other similar methods (Lin *et al*., 2014). These applications indicate that γ-PGA can be used not only for the removal of pollutants from wastewater, but also for the development of monitoring systems for environmental contaminants.

5.3. Biological adhesive

Bioadhesives are used for tissue adhesion and for sealing air or fluid leaks during surgery. Although fibrin remains the most widely used biological adhesive, gelatin/PGA hydrogels have emerged as a promising alternative. Studies have shown that these hydrogels exhibit good biocompatibility, rapid curing and resistance to pressure, supporting their potential use in lung surgery. The material degrades naturally after tissue healing and is typically prepared using 1-(3-dimethylaminopropyl)-3-(ethylcarbodiimide) hydrochloride (EDC) as a crosslinking agent (Otani *et al*., 1999).

5.4. Biopolymer flocculant

γ-PGA exhibits good flocculating activity in the presence of di- and trivalent cations. Its ability to flocculate depends on polymer concentration, cation concentration and pH of the medium (Bajaj and Singhal, 2011a). To improve these properties, γ-PGA can be crosslinked by γ-ray irradiation. Cross-linked γ-PGA shows better flocculation properties than native γ-PGA and has lower turbidity. Similarly, the addition of trivalent cations leads to an increase in flocculation, while this effect is absent with monovalent and divalent cations. These properties may present an environmentally friendly option to replace

synthetic flocculants, which can be toxic and sometimes cannot be degraded (Taniguchi *et al*., 2005).

5.5. Anticorrosive applications

Another potential application is the use of γ-PGA as a main component in the preparation of anticorrosive composites. Due to its biodegradable and non-toxic character, it can be an environmentally friendly alternative to traditional chemical inhibitors. Moreover, the composite is stable to variations in temperature, pH and salinity concentration, providing long-lasting corrosion protection. The protection mechanism works in two stages. In the first stage, γ-PGA forms a protective layer on the metal surface, preventing the action of corrosive agents, and in the second stage the composite binds to mineral ions such as Ca^{2+} and Mg^{2+}, preventing nucleation and crystal growth. Tests have shown long-term stability even in hard water conditions (Chen *et al*., 2015).

5.6. Medical applications

5.6.1. Drug delivery systems

Medical and pharmaceutical applications represent one of the most actively studied fields of γ-PGA research. Owing to its biocompatibility, biodegradability and the presence of multiple reactive carboxyl groups, γ-PGA can be modified for a variety of biomedical purposes, including drug delivery, tissue engineering and wound healing. Recent developments in nanotechnology have further expanded its potential by enabling the design of multifunctional delivery systems with improved therapeutic performance. The main use of polyglutamic acid in the medical field is for the controlled or prolonged administration of active ingredients. For this purpose, the most used method involves the fabrication of nanocapsules made of or containing polyglutamic acid, which encapsulate the bioactive compound.

He et al. (2023) developed γ-PGA/tannic acid-based nanoparticles for the sustained delivery of doxycycline in oral ulcer therapy. The nanocarrier combined antibacterial activity, immunomodulatory effects, and prolonged drug release, resulting in enhanced therapeutic performance. The nanoparticles exhibited strong adhesion to ulcerated tissue, as well as a sustained antibiotic release at the wound site. This results in more effective inhibition of bacterial activity at the ulcer site, as well as a reduction in the excessive inflammatory response (He *et al*., 2023).

The ideal method of drug delivery is oral, but peptides with medicinal properties, such as insulin, have the disadvantage of being unstable at the acidic pH of the gastric system. In this context, Lin et al. studied the encapsulation of insulin in polyglutamic acid nanoparticles coated with chitosan. Nanoparticles

are designed to protect insulin from enzymatic degradation in the gastrointestinal tract and improve its absorption. Polyglutamic acid contributes to the structural stability of the nanoparticles and facilitates efficient insulin embedding, while chitosan, known for its mucoadhesive properties, provides enhanced interaction with the intestinal mucosa. The resulting system allows a controlled release of insulin, which helps to maintain stable plasma concentrations and reduce blood glucose fluctuations. The study results highlight that PGA-chitosan nanoparticles offer a promising alternative to oral insulin delivery, improving both therapeutic efficacy and patient comfort by eliminating the need for daily injections (Lin *et al.*, 2007). In 2019, Urimi et al. (2019) made poly(sodium-4-styrenesulfonate) (PSS) crosslinked chitosan nanoparticles, subsequently functionalized with PGA, for insulin encapsulation. The developed nanoparticles demonstrate prolonged drug release under different pH conditions and a superior drug uptake to non-functionalized nanoparticles. Also, the pharmacological availability of insulin administered by these functionalized nanoparticles is significantly higher compared to that of nanoparticles made of chitosan and PGA or chitosan and PSS: 17.3 ± 0.9% versus 10.9 ± 1.5% and 12.9 ± 1.8% (Urimi *et al*., 2019).

L-phenylalanine-conjugated polyglutamic acid nanoparticles were designed in 2005 by Akagi et al. for use as protein carriers. They showed a high protein-binding capacity and a prolonged and controlled release profile. L-phenylalanine-conjugated polyglutamic acid amphiphilic nanoparticles were used by Ryu *et al*. (2011) for dexamethasone embedding. In this way, the active compound, with its phagocytic cell-suppressing properties, can be administered directly into the affected retinal tissues, reducing inflammation and excessive immune cell activity. For the treatment of malaria, Hoennscheidt *et al*. (2013) have realized the encapsulation of the low water-soluble quinine in polymeric γ-PGA matrices modified with l-phenylalanine ethyl ester. The result was a stable quinine nanodispersion based on esterified γ-PGA.

Another area of interest is the development of γ-PGA-based systems for antifungal drug delivery. In this context, Zia et al. (2015) investigated the possibility of using self-assembled PGA-based nanoparticles to deliver amphotericin B. This broad-spectrum antifungal agent has a major drawback in terms of prolonged administration, often imperative for certain treatment regimens, namely the nephrotoxicity associated with the high dosage of the drug. To combat this issue, the authors propose the development of nanoparticles with PGA, taking advantage of amphotericin B's tendency to aggregate in aqueous media. The study revealed an antifungal capacity of AmB-PGA nanoparticles similar to other formulations on the market, but with superior colloidal stability in physiological media, as well as a prolonged release profile that reduces the burst effect present in the other cases (Zia *et al*., 2015).

The studies presented above show that γ-PGA can be successfully adapted for a wide range of drug delivery applications. Whether used for antibiotics, proteins, antifungal agents or antimalarial drugs, the polymer

contributes to improved stability and controlled release of the active compounds. These findings show that γ-PGA-based systems may represent useful alternatives to conventional formulations, although additional studies are still needed before large-scale pharmaceutical implementation becomes feasible.

5.6.2. Oncologic treatments

Although there are various studies on the development of drug conjugates with polyglutamic acid through linkages involving the carboxyl groups of the polymer side chains (Li, 2002), the current direction of study is the use of biopolymers for the controlled delivery of active ingredients. A broad field of application arises in anti-cancer therapy, where substances with an anti-proliferative role on tumour cells also have multiple negative effects on healthy tissues.

Since the discovery of its anti-cancer properties in 1965, cisplatin has become the most widely used cancer treatment. However, it has severe side effects such as nephrotoxicity, ototoxicity or peripheral neuropathy, which is why various studies have been carried out to improve the clinical applications of the drug. In 2012, Song et al. studied the incorporation of cisplatin into methoxypolyethylene glycol-block-poly-L-glutamic acid (mPEG-b-PLG) micelles. The resulting drug achieved a cytotoxicity similar to that of free cisplatin over a much longer time, thus allowing higher doses to be administered and extending the duration of pharmacologic effect. Their antitumour activity has been investigated in vivo using lung adenocarcinoma-infected cells, observing an inhibitory effect on tumour volume growth and a prolongation of the lifespan of the test animals, correlated with a lower toxicity (Song *et al*., 2012). Another variant was studied in 2020 by Wang et al, who propose the use of a tetravalent platinum-based prodrug. This offers the possibility of restoration to the active platinum (II) form intracellularly, but with much greater stability. The authors developed nanoconjugates based on polyglutamic acid modified with citric acid and a platinum (IV)-based prodrug, obtaining particles that retain antitumour activity, and exhibit longer release time and lower cytotoxicity compared to cisplatin (Wang *et al*., 2020).

Doxorubicin (DOX) is another active pharmaceutical ingredient used in the treatment of cancerous tumours, which, when administered conventionally, induces adverse effects on both the cardiac and gastrointestinal systems. Administration of doxorubicin in the form of nanoparticles has the ability to reduce the toxicity of the drug and, due to its small size, increases the transport capacity of the active compound to the tumour, where a prolonged release of the drug occurs. Hellmers et al. (2013) studied the development of γ-PGA nanoparticles for use as doxorubicin transport vehicles. They observed that although there is electrical charge compatibility between DOX and γ-PGA, the mixture does not form nanoparticles. But if chitosan is added to the complex,

relatively spherical particles are formed, with an encapsulation efficiency of up to 70%. The polyglutamic acid and chitosan nanoparticles do not show cytotoxicity, and the doxorubicin-loaded nanoparticles obtained show anti-proliferative properties on cancer cells (Hellmers *et al*., 2013). In 2016, Tukappa et al. (2016) realized the embedding of doxorubicin in mesoporous silica nanoparticles coated with polyglutamic acid. The polymer coating allows controlled release of the active principle, degrading in the presence of enzymes capable of hydrolysing peptide bonds.

The development of PGA amphiphilic nanocapsules with a lipid centre and hydrophilic coating is also additionally being studied for the administration of substances with antitumour activity but low solubility in aqueous media, while investigating the possibility of controlled or prolonged administration. In this regard, Gonzalo et al. (2013) have realized the encapsulation of plitidepsin in polyglutamic acid nanoparticles grafted with polyethylene glycol (PGA-PEG) and Lollo et al. (2014) have realized PGA-PEG nanocapsules containing 57% PEG loaded with docetaxel.

In vitro or in vivo techniques can be used in gene therapy, with promising applications in the treatment of genetic diseases or non-heritable diseases such as cancer or AIDS. In vivo gene delivery can be achieved using viral vectors, which have high transfection efficiency but high toxicity and immunogenicity, or using non-viral vectors, which is the direction in which several studies are heading. For this purpose, nanocomposites based on polyethyleneimine and γ-polyglutamic acid were developed, the latter serving to improve cytocompatibility and reduce toxicity. Tripathi et al. (2011) analysed the influence of the ratio between polyethyleneimine and γ-PGA in nanocomposites obtained by electrostatic interaction between the two polymers, then loaded with nucleic acid fragments. They observed a significant increase in cell viability compared to polyethyleneimine (PEI) in vitro studies and compared to Lipofectamine in *in vivo* studies.

The available studies suggest that γ-PGA-based nanocarriers may offer important advantages in cancer therapy, particularly by reducing systemic toxicity and improving drug accumulation at the tumour site. Although the experimental results are encouraging, most investigations are still limited to laboratory or animal studies. Further research is therefore necessary to determine whether these systems can achieve similar benefits in clinical practice.

5.6.3. Bone repair

Traditional bone cements, although widely used, have limitations such as poor biocompatibility, poor osseointegration and mechanical degradation. For this reason, studies have been carried out to minimize these disadvantages. The hybrid bone cement based on γ-PGA and tricalcium silicate (C3S) has attracted attention as a potential material for bone regeneration because it combines the

mechanical strength of C3S with the biocompatibility of γ-PGA (Chung *et al*., 2017).

Another composite with bone regeneration properties is chitosan/ γ-PGA, which combines bone regeneration with antimicrobial properties. Experimental results have demonstrated that the structure of the chitosan/γ-PGA skeleton exhibits a porosity that allows the diffusion of nutrients and cells essential for osteogenesis. At the same time, the material exhibits optimal mechanical strength, which makes it possible to support the repair of bone defects. Throughout the experiment, the material inhibited the growth of bacteria such as Staphylococcus aureus and Escherichia coli. Thus, the material based on chitosan and γ-PGA represents a potential alternative to treat dental bone defects (Wu *et al*., 2012).

5.6.4. Other medical applications

γ-PGA has other potential medical applications. A hydrogel based on γ-PGA and konjac gum (KGM) is an innovative material for the treatment of severe skin wounds. γ-PGA improves water retention and promotes cell regeneration and KGM provides high structural stability and elasticity. Experimental results show good antimicrobial activity, preventing the growth of bacteria such as Staphylococcus aureus and Escherichia coli. In vitro tests demonstrate good adhesion and proliferation of fibroblasts, and in vivo tests show a decrease in the time it takes to close wounds and the formation of new tissue with minimal risk of scarring (Zhu *et al*., 2021).

γ-PGA can also be used to create a composite with virus adsorbing properties. Sun et al. (2020) developed a biocomposite based on cellulose microfibres (CMF), γ-PGA and mesoporous silica nanoparticles (MSNs) for the adsorption of Enterovirus 71. In this material, CMF acts as a structural support, γ-PGA contributes through its affinity for proteins and viral particles, while MSNs increase the available adsorption surface. The results showed efficient virus removal under conditions close to physiological pH, together with good biocompatibility and low cytotoxicity.

γ-PGA can also be used to make nanofibers, which have potential applications in the creation of porous scaffolds for skin, bone and tissue regeneration, wound dressings and drug delivery systems (Wang *et al*., 2012).

5.7. Food industry applications

γ-PGA hydrogel prolongs the shelf life and improves the quality of shiitake mushrooms by minimizing decomposition and water loss. The hydrogel, prepared by Tao et al by cross-linking with polyethylene glycol diglycidyl ether (PGDE), increased the shelf life of the mushrooms from 8 days to 30 days at 4°C (Tao *et al*., 2021). The use of polyglutamic acid to increase shelf life can also be

achieved at low temperatures. Analyses performed on crayfish treated with γ-PGA revealed significant improvements in sensory properties and superior quality compared to untreated crayfish, even after extended storage periods. Treatment with γ-PGA at 2% and 4% concentrations resulted in a 10% increase in the water-holding capacity of muscle fibres, preventing dehydration and the appearance of large ice crystals (Abdelnaby *et al*., 2023). Polyglutamic acid can also be used as a cryoprotectant for surimi. It effectively regulates protein oxidation, making it a useful additive for protecting protein-based products in freeze-thaw conditions (Yan *et al*., 2024).

5.8. Cosmetics applications

Polyglutamic acid has certain properties that make it suitable for the cosmetics industry. Due to its humectant properties, moisture retention capacity, and biocompatibility, it emerges as a promising candidate for addressing various hair-related issues. Kim et al. (2019) developed PGA/chitosan nanoparticles with the aim of encapsulating plant extracts in order to improve the hair growth process. The use of ultra-high molecular weight PGA can also lead to an increase in the size of hair follicles and improve their activity. Combining this ability with the moisturizing properties of PGA, it could be used to treat alopecia (Choi *et al*., 2014).

To alleviate dry mouth, the use of a γ-PGA-based oral spray has been investigated, as it helps hydrate the oral mucosa. This spray also helps maintain an optimal pH of the oral cavity, which may help prevent caries (Yamamoto *et al*., 2016).

A comprehensive summary of the biosynthesis, structural characteristics, fundamental properties and diverse applications of γ-PGA discussed above is presented in Table 2.

Table 2

Overview of γ-PGA biosynthesis, structure, properties and applications

Application field	Main role of γ-PGA	Advantages	Limitations	Representative references
Agriculture	Soil remediation, fertilizer efficiency, plant growth stimulation	Biodegradable, improves soil structure and microbial diversity	High production costs and limited industrial-scale use	Pereira *et al*. (2017) Mu *et al.* (2021) Guo *et al*. (2024) Bai *et al.* (2020) Ngearnpat *et al*. (2023) Zeng *et al*. (2024)
Wastewater treatment	Adsorption of heavy metals and pollutant sensing	High adsorption capacity, eco-friendly, sensitive contaminant detection	Requires composite formulations for enhanced stability	Mu *et al.* (2018) Inbaraj *et al*. (2009) Lin *et al.* (2014)

Tissue adhesives	Surgical hydrogel adhesives and sealing materials	Fast curing, biocompatibility, biodegradability	Mechanical optimization still required	Otani *et al*. (1999)
Flocculants	Water clarification and particle aggregation	Sustainable alternative to synthetic flocculants	Strong dependence on pH and ionic composition	Bajaj and Singhal (2011a) Taniguchi *et al.* (2005)
Anticorrosive materials	Corrosion and scale inhibition	Non-toxic, stable in saline and variable pH conditions	Limited industrial implementatio n studies	Chen *et al*. (2015)
Drug delivery systems	Controlled and sustained release of drugs	Improved bioavailability and prolonged release	Complex preparation methods	He *et al*. (2023) Lin *et al.* (2007) Urimi *et al.* (2019) Akagi *et al.* (2005) Ryu *et al*. (2011) Hoennscheidt *et al.* (2013) Zia *et al*. (2015)
Anticancer therapy	Nanocarriers for anticancer agents	Reduced systemic toxicity and enhanced tumour targeting	Clinical translation remains limited	Song *et al.* (2012) Wang *et al.* (2020) Hellmers *et al*. (2013) Tukappa *et al*. (2016) Gonzalo *et al.* (2013) Lollo *et al.* (2014)
Gene therapy	Non-viral delivery vector component	Improved cytocompatibility and reduced toxicity	Lower transfection efficiency than viral vectors	Tripathi *et al.* (2011)
Bone regeneration	Bone scaffolds and hybrid cements	Osteointegration and controlled biodegradation	Mechanical limitations compared to conventional biomaterials	Chung *et al.* (2017) Wu *et al.* (2012)
Wound healing	Injectable hydrogels and antimicrobial dressings	Promotes tissue regeneration and inhibits bacterial growth	Requires further in vivo and clinical validation	Zhu *et al.* (2021)
Viral adsorption	Adsorption and removal of viral particles	High adsorption efficiency and low cytotoxicity	Early-stage experimental development	Sun *et al.* (2020)
Nanofibers and scaffolds	Tissue engineering and regenerative medicine	High porosity and biocompatibility	Fabrication scalability challenges	Wang *et al.* (2012)
Food industry	Cryoprotectant and preservation agent	Improves shelf life and water retention	Economic feasibility for large-scale applications	Tao *et al.* (2021) Abdelnaby *et al.* (2023) Yan *et al.* (2024)

Cosmetics	Moisturizing and hair-growth formulations	Excellent humectant and biocompatible properties	Limited clinical studies	Kim *et al*. (2019) Choi *et al.* (2014)

Table compiled and adapted by the authors based on the literature reviewed in this study.

6. Challenges and future perspectives

Despite the wide range of applications reported for γ-PGA, several limitations still restrict its large-scale use. The economic viability of γ-PGA production remains a challenge, mainly because fermentation, purification and downstream processing require significant resources and operational costs. In addition, many Bacillus strains produce limited amounts of polymer, reducing the economic attractiveness of industrial production. Although genetic engineering approaches have improved productivity, further optimization is still required before γ-PGA can become a widely accessible industrial biopolymer.

A further limitation is the difficulty of obtaining γ-PGA with consistent characteristics, as factors such as fermentation conditions and nutrient composition can influence both molecular weight and stereochemical composition. Parameters such as pH, aeration, fermentation time, and nutrient composition significantly affect polymer characteristics, making process standardization difficult. Therefore, the development of robust and controllable biosynthesis strategies remains essential for obtaining γ-PGA with reproducible quality suitable for biomedical and pharmaceutical applications.

In the biomedical field, γ-PGA-based nanomaterials demonstrate excellent biocompatibility and promising drug delivery capabilities; however, additional in vivo studies and clinical trials are necessary to fully evaluate their long-term safety, biodegradation behavior, pharmacokinetics, and potential immunogenicity. Regulatory approval also represents a considerable obstacle for the clinical translation of γ-PGA-based systems.

From an environmental and industrial perspective, future research should focus on the use of renewable and low-cost substrates, including agricultural and food-processing wastes, in order to reduce production expenses and improve sustainability. Moreover, the combination of γ-PGA with other biopolymers, nanoparticles, or functional materials may lead to the development of advanced multifunctional composites with enhanced mechanical, antimicrobial, adsorption, or therapeutic properties. Future developments in biotechnology and materials science will likely contribute to a broader use of γ-PGA in industrial and biomedical applications.

The successful commercialization of γ-PGA will depend not only on improvements in production efficiency, but also on the development of economically competitive manufacturing processes capable of meeting industrial quality requirements.

7. Conclusions

This review summarizes the main characteristics, production methods and applications of γ-PGA, emphasizing its growing importance as a sustainable microbial biopolymer. From agriculture and medicine to environmental remediation and cosmetics, γ-PGA demonstrates a wide range of applications due to specific properties such as non-toxicity, biocompatibility and biodegradability. However, high production costs, low biosynthetic yields, purification difficulties and process standardization challenges remain major limitations that restrict its widespread industrial applications. Future approaches, such as optimizing fermentation processes, using renewable agricultural waste as feedstock and developing advanced metabolic engineering and bioprocess technologies, may contribute to reducing production costs and improving the large-scale accessibility of this biopolymer. The growing number of studies published in recent years suggests that γ-PGA will continue to attract interest in both industrial and biomedical research. Improvements in production efficiency may facilitate its broader practical use in the future.

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ACIDUL POLIGLUTAMIC: UN BIOPOLIMER INOVATOR ȘI MULTIFUNCȚIONAL

(Rezumat)

Acidul poliglutamic (γ-PGA) este un biopolimer microbian biodegradabil și prietenos cu mediul, remarcat pentru proprietăți precum biocompatibilitatea, biodegradabilitatea și versatilitatea sa. Lucrarea prezintă principalele caracteristici structurale ale γ-PGA, metodele de obținere și domeniile sale de aplicare. În agricultură, acest biopolimer poate contribui la îmbunătățirea fertilității solului, la creșterea eficienței îngrășămintelor și la remedierea solurilor afectate de salinitate. În domeniul medical, γ-PGA este utilizat în sisteme de administrare controlată a medicamentelor, adezivi biologici și materiale pentru regenerarea osoasă. De asemenea, proprietățile sale de adsorbție și floculare îl recomandă pentru tratarea apelor contaminate și pentru alte aplicații de protecție a mediului. În industria alimentară și în cea cosmetică, γ-PGA este valorificat datorită capacității sale de hidratare și efectului crioprotector. Cu toate acestea,

costurile ridicate de producție și randamentele limitate ale proceselor de biosinteză reprezintă încă obstacole importante pentru utilizarea sa pe scară largă. Pe baza studiilor analizate, γ-PGA reprezintă un biopolimer cu perspective importante, iar extinderea aplicațiilor sale va depinde însă de dezvoltarea unor metode de producție mai eficiente și mai sustenabile.