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Review

Progress in the Biomedical Application of Biopolymers: An Overview of the Status Quo and Outlook in Managing Intrauterine Adhesions

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Abstract: Advancements in material science have made biopolymers a reliable solution in treating diseases for which there were no effective treatments. Intrauterine adhesions (IUAs) are the second leading cause of secondary infertility among women of reproductive age. Despite their negative impacts, the available data reveal that there is currently no effective treatment. This work serves to provide an overview of the progress in the biomedical application of biopolymers focusing on the clinical management of IUAs. Hysteroscopic adhesiolysis remains the standard treatment for IUAs, even though it is linked to recurrence and suboptimal reproductive outcomes. Efforts to improve IUAs treatment by combining hysteroscopy with adjuvants like physical barriers have not resulted in better outcomes. Biopolymers like hyaluronic acid (HA) represent a groundbreaking shift in regenerative medicine and have been used as anti-adhesives in the treatment of IUAs. This is attributed to their excellent biocompatibility, cell adhesiveness, biodegradability, low toxicity, and cell growth promotion ability. This study examines naturally occurring biopolymers, underscoring their biomedical applications, and limitations such as poor mechanical properties, rapid degradation, limited residence time, and bioavailability. Drawing from existing evidence and authors' standpoints, innovative approaches harnessing the power of biopolymer engineering are suggested as future directions to overcome ongoing limitations.

Keywords: biopolymers; intrauterine adhesions; Asherman's syndrome; hyaluronic acid; biomaterials; chemical crosslinking

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1. Introduction

Recent progress in medical technology, material science, and tissue engineering has opened new possibilities for treating some of the most debilitating diseases, including damage to or loss of tissues and organs. As a result, patients can now benefit from clinically active biopolymer-based materials, leading to tissue regeneration and the restoration of lost biological functions [1]. Researchers have shown that biopolymers (also known as biomaterials) may have invaluable roles in managing reproductive system disorders, notably IUAs. These materials can help protect the endometrial lining, restore damaged tissues and improve reproductive health pre- and post-intrauterine surgeries. This is owed to their inherent properties and therapeutic potentials [2]. To achieve this, biopolymers are endowed with excellent physicochemical and mechanical properties, in addition to their propensity to accept modifications mainly via crosslinking or bioconjugations [1,3].

The latter is very important because it has led material scientists and polymer engineers to manipulate biopolymers with the focus of improving their properties and widening their applications in various fields, including regenerative medicine.

Biopolymers are a subtype of polymers sourced from living organisms, such as plants and animals, and are made of long chains of small repeating units called monomers [4]. These macromolecules have interesting biological properties, including biocompatibility, biodegradability, low toxicity, minimal immune response, strong cell growth promotion ability, and good cell adhesiveness [1,5–7]. Table 1 summarises key properties of biomaterials currently applied in the field of reproductive medicine and tissue engineering. These distinct properties of biopolymers make them highly suitable for various biomedical applications, such as in regenerative and reproductive medicine, tissue engineering, drug delivery, and immunotherapy [2,6,8].

Table 1. Desirable characteristics of biomaterials for use in tissue engineering applications.

Characteristics	Descriptions
Biocompatibility	Biomaterials should not trigger adverse immune responses when interacting with the body, while also providing biological and functional benefits to the construction.
Biodegradability	After interacting with the body, the biomaterial should degrade, and either be excreted or absorbed by the body.
Lack of toxicity	The by-products generated by biomaterials should be non-toxic and pose no harm to the body or surrounding tissues.
Lack of immunogenicity	Biomaterials should not trigger a significant immune response when they are introduced into the body.
Cell adhesiveness	Biomaterials should have the ability to adhere to tissues in the body to effectively carry out their physiological functions.
Cell growth promotion	Biomaterials should support, enhance or stimulate cell growth, attachment and proliferation once in contact with the body's injured area.
Mechanical properties	Biomaterials should have strong mechanical properties that match the structure of reproductive organ tissues and support their functions effectively.
Biomimicry	Biomaterials should be designed to align with the anatomical and physiological characteristics of specific native tissues.

Infertility is a worldwide health issue that impacts approximately 8–10% of couples and is mainly linked to ovulatory or menstrual disorders [9]. IUAs are the second-most-common cause of secondary infertility in women of reproductive age, and finding effective treatments for this condition continues to be a critical challenge [10,11]. This debilitating condition not only impairs female reproductive potential by provoking pathophysiological changes in the intrauterine cavity, but also has significant physical, psycho-social, and economic effects [12,13]. Discomforts among affected women are often associated with infrequent or painful menses, recurrent miscarriages, or infertility [14]. Also, in some instances, severe adhesions in the uterus can prevent embryo implantation or disrupt foetal development [15]. Despite the growing incidence of IUAs, there are currently no effective preventative or therapeutic options available. It was recently reported that the lack of effective IUAs treatment is linked to the complexity of the uterus' anatomical structure and internal environment, as well as varying physiological functions [16]. Additionally, although various management strategies have been proposed, each faces significant limitations that prevent their widespread translational application in routine clinical care.

IUAs are acquired endometrial conditions characterised by fibrosis and the formation of scar tissue bands (also called adhesions) in the wall lining the uterine cavity [17]. They

result from trauma to and inflammation of the endometrium precisely during different types of surgical operations or due to microbial infections such as tuberculosis (TB) and schistosomiasis [2,15,18]. Similarly, abdominal and pelvic surgeries have been identified as the leading cause of peritoneal adhesions and continue to contribute significantly to patient morbidity. Studies show that adhesions develop in approximately 66–79% of patients who undergo these types of procedures [19]. Regarding the adhesions occurring inside the uterus, although the terms IUAs and Asherman's syndrome are frequently used interchangeably, Deans and Abbott, (2010) clarified that IUAs are the leading causes of Asherman's syndrome [20]. Figure 1 illustrates the main causes of IUAs and their current treatment approaches. The negative effects of IUAs become more severe when they affect women of childbearing age, where the condition can lead to complete infertility along with physical and mental health problems [14].

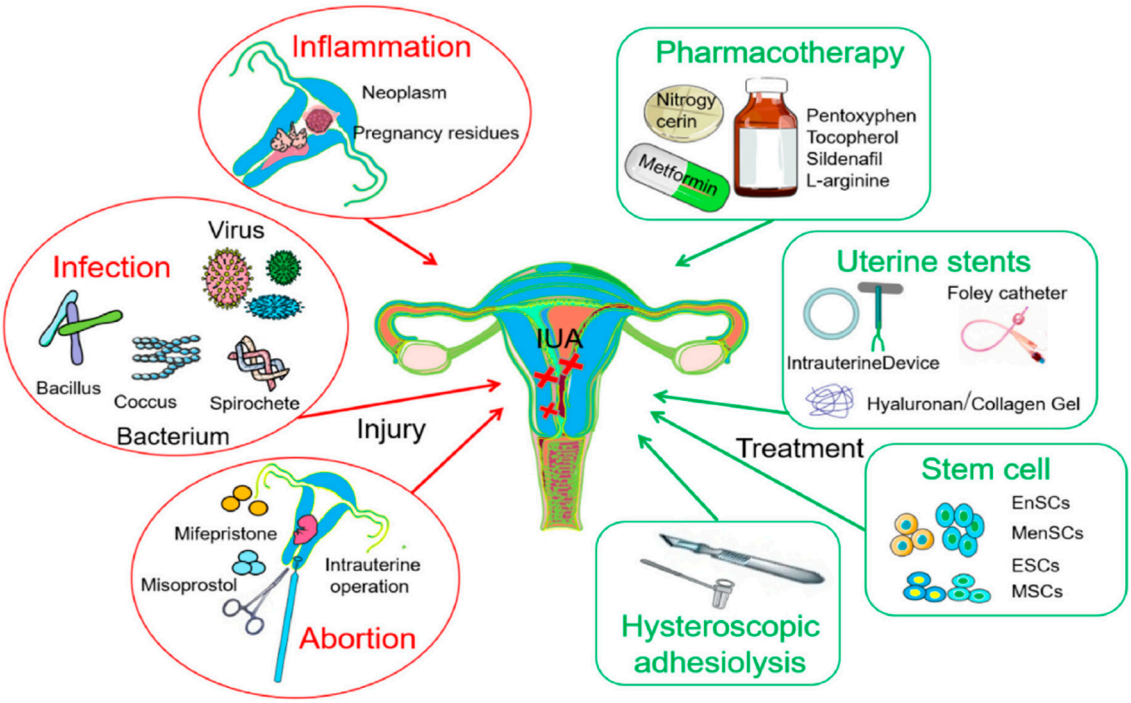


Figure 1. The common causes of IUAs and current treatment methods. IUAs commonly result from endometrial injury, inflammation or infections. While hysteroscopy is the standard treatment, current additional management methods include pharmacotherapy, stem cell therapy, and physical barriers. Adapted from [18]. Red 'X' indicates adhesions, 'red outline sections' indicate causes of adhesions, 'green outlines' indicate treatment of adhesions.

The pathology of most IUAs involves a noticeable inflammatory response that impairs angiogenesis and inhibits new blood vessel formation (angiogenesis), while encouraging the development of adhesions [21]. Also, during the study conducted to elucidate the pathophysiology of Asherman's syndrome using single-cell RNA sequencing technology, it was revealed that the development of IUAs is marked by the loss of endometrial epithelium, disruptions in key signalling pathways like Wnt and Notch which regulate epithelial differentiation, and the presence of secretory leukocyte protease inhibitor-expressing epithelium during implantation. Given the relevance of cell-to-cell communication in keeping homeostatic control of the endometrium [22], impaired cell signalling and gene expression translate into a dysfunctional environment that promotes fibrosis, inflammation, and inhibits angiogenesis [23]. These molecular biology clues are critically important, as they provide a deeper understanding of the underlying mechanisms of IUAs. Such knowledge can serve as a foundational step toward the development of precise, targeted

therapies aimed at preventing or reversing adhesion formation, ultimately improving patient outcomes.

In terms of how IUAs impair female reproductive potential, they interfere with key reproductive processes such as fertilisation and overall reproductive function. It is suggested that IUAs obstruct the movement of sperm from the cervix through the uterus to the fallopian tubes, and hinder embryo implantation and placental development. Moreover, scarring within the uterus contributes to abnormal decidualization and atypical trophoblastic infiltration, which can lead to placental attachment disorders. Therefore, it is strongly advised that all preventive measures aiming at avoiding damage to the basal layer of the endometrium be applied in order to preserve its structural integrity and receptivity, thereby protecting female fertility [24].

Some risk factors may predispose women to developing IUAs. These include pregnancy, having postpartum uterus, and repeated uterine injuries from medical procedures [24–26]. Various studies reported that women undergoing hysteroscopic myomectomy face a significant risk of developing IUAs, underscoring the importance of primary prevention to safeguard female reproductive health [13,27,28]. A study assessing the prevalence of IUAs in women with a history of miscarriage found that repeated miscarriages, elective pregnancy terminations, and dilatation and curettage procedures are among the major risk factors for IUAs development. These procedures often cause mechanical trauma to the endometrial lining, increasing the likelihood of fibrosis or adhesion formation [29].

Prognosis and reproductive outcomes for women with IUAs depend on both the treatment approach and the disease's clinical stage. For instance, managing mild-to-moderate IUAs can be simpler and yields better outcomes compared to severe IUAs. Henceforth, raising awareness of IUAs, ensuring early detection, and focusing on primary prevention are crucial for the management of IUAs [13,14]. Likewise, there is an urgent need for an effective health technology to effectively prevent and treat IUAs, improve women's quality of life, and safeguard reproductive health. This solution should either prevent the initial formation of IUAs or, if adhesions are already present, enable scar-free endometrial regeneration without the risk of adhesions recurrence. Table 2 summarises some common risk factors predisposing women to IUAs.

Table 2. Common risk factors predisposing women to the development of IUAs.

Risk Factors	Rate of IUAs	Reference
Hysteroscopic myomectomy	39.0%	[13]
D&C procedure	30.6%	[30]
C-section	1–4%	[14]
Pregnancy termination	10–40%	[14]
Abortions	6–30.0%	[15]
Repeated miscarriages	20.0%	[29]

To date, hysteroscopic adhesiolysis is regarded as the gold standard for treating IUAs and has been effective in removing adhesions followed by endometrial regeneration [31]. Hysteroscopy is a painless, minimally invasive procedure for diagnosis and treatment of IUAs [32]. After a physician identifies adhesions through diagnostic hysteroscopy, hysteroscopic adhesiolysis is performed to remove them and alleviate related symptoms while ensuring restoration of the anatomical integrity of the uterus via endometrial regeneration. Prior to this, the physician determines the disease prognosis to guide decision-making on a comprehensive approach that includes preoperative, intraoperative, and postoperative

strategies, as well as procedures designed to prevent adhesion recurrence and ensure optimal fertility outcomes [33].

However, it was reported that in some conditions hysteroscopic adhesiolysis is associated with a high recurrence rate [15,31]. Several studies reported that the recurrence rate of IUAs after hysteroscopic adhesiolysis ranges from 20% to 62.5%, and this is often associated with poor reproductive outcomes [15,24,31,33,34]. Poor reproductive outcomes are largely due to complications such as spontaneous abortions, preterm delivery, intrauterine growth restriction, placenta accreta, and, in severe cases, uterine rupture [34]. There are various medical approaches available to manage the consequences of IUAs or uterine cancers treated through hysteroscopy. These include uterus transplantation and surrogacy. However, ethical concerns, technical and safety issues, as well as the risk of life-threatening tissue rejection continue to be substantial barriers [35,36].

Recently, improvement was made to improve IUAs management by combining hysteroscopic adhesiolysis with physical barriers, hormone therapy, or stem cell therapy [17,20]. However, the translational use of these approaches faces several challenges. For instance, physical barriers may not be patient-specific to match diverse shapes and sizes of uteruses, and metal-based intrauterine devices (IUDs) were associated with microbial infections [18,37]. Also, although hormone therapy with oestrogen has been used to manage IUAs, its low solubility results in limited drug bioavailability and thus, reduced therapeutic effect [38,39]. Chi et al., (2018) revealed that while oestrogen alone can prevent the formation of adhesions, it has limited effectiveness in improving reproductive outcomes. However, in the same study, when oestrogen was combined with aspirin, it promoted endometrial regeneration and reduced the recurrence of adhesions. Despite these benefits, prolonged use of oral oestrogen can lead to various negative side effects, such as an increased risk of breast cancer, especially in individuals with higher levels of oestrogen receptor alpha (ERα) [40]. Likewise, extended use of oestrogen and progesterone may cause hormonal imbalances, contributing to issues such as breast and cervical cancers, thrombosis, neurological disorders, and further infertility [41]. Table 3 presents some advantages and drawbacks of current IUAs management strategies.

With the mounting advances in material science and bioengineering, biopolymers can be modified to improve their capacities and applicability in the clinical management of IUAs [2,27,43]. This has the potential to play a significant role in the discovery of innovative treatments and health technologies for a range of evolving and complex medical conditions, including IUAs. Thus, by advancing our understanding and ability to leverage material science and bioengineering in targeting such conditions, it could pave the way for more effective and tailored therapies, improving patient outcomes and offering novel solutions for even other conditions that have long been threatening human lives worldwide.

Biopolymers such as HA-based hydrogels were reported effective in promoting endometrial regeneration and improving reproductive outcomes after hysteroscopy. However, HA's therapeutic effect is limited by its quick degradation by endogenous hyaluronidases, which reduce its residence time at the treatment site, bioavailability and, therefore, its therapeutic potential [7]. Effort was made to improve the properties of this biopolymer such as chemical modification by crosslinking [45,46]. However, this could not completely resolve these issues, given the nature of HA and its extensive biomedical applications. Also, a recent study by Buckley et al. (2024) reported that chemical modifications of HA produced a 3D-printed thiolated HA hydrogel, which showed a tailorable degradation profile, a necessary attribute for any medical device [47]. Thus, it is essential to build on existing evidence and expand our horizons to envision innovative health technologies that harness the power of biopolymers, like HA, to effectively prevent and treat IUAs. These advancements can enhance overall female reproductive health and well-

being and reduce the economic burdens related to IUAs, while contributing to sustainable development goals.

Table 3. Advantages and drawbacks of the common IUAs management strategies.

Treatment	Advantages	Disadvantages	Reference
Hysteroscopy	Adhesions Removal Endometrial Regeneration Improve reproductive outcomes	Recurrence	[15,41]
Physical barriers (IUD and Foley catheter balloons)	Recovery of menstrual volume Relatively prevent re-adhesions	No effects on reproductive outcome Risk of microbial infection Lack of patient-specificity regarding diverse shapes and sizes of uteruses	[17,34]
Biomaterials (Hydrogels) plus hysteroscopy	Prevent re-adhesions Endometrial regeneration Improve reproductive outcomes	Rapid enzymatic degradation Reduced residence time in uterus Issues related to their administration	[7,15,42]
Hormones (oestrogen and progesterone)	Adhesion prevention	Minimal impact on improving reproductive outcomes Low solubility and limited bioavailability (oestrogen) Increased risk of breast and cervical cancers, thrombosis, neurological effects, and infertility	[39]
Stem cell therapy	Adhesion prevention Endometrial regeneration Reproductive outcome	High colonization rates, long-term effectiveness, promoting tumorigenesis Immune rejection due to allogeneic sources of the cells Reduced retention time at active site once administered intravenously Ethical issues	[18,43,44]

Equally important, there is a need for continued research and development to modify clinically important biomaterials, particularly HA, to enhance stability and biocompatibility, lower cytotoxicity, and better suit current and future medical needs [7,15,47]. Furthermore, regarding IUAs management, attention should be directed not only towards chemical modifications but also the development of polymer bio-composites and the use of different dosage forms, such as solid dispersions and implants [48,49], while carefully considering high diversity in sizes and shapes of the uteruses. These strategies could potentially improve residence time at the target site, enhance bioavailability, and increase the therapeutic efficacy of the administered HA biopolymer.

This review aims to discuss the progress in the biomedical application of biopolymers focusing on the status quo and outlook in managing IUAs. It also examines current treatment strategies, emphasising the existing gaps, and suggesting innovative approaches that utilise cutting-edge technologies in material science to effectively manage IUAs and improve female reproductive health and quality of life. Despite the promising results from the current therapeutic approaches for IUAs, such as hysteroscopic adhesiolysis combined with antiadhesive biopolymers like crosslinked HA hydrogels, significant challenges persist, including high recurrence rates and limited reproductive outcomes. As a result, based on the existing literature and the authors' viewpoints, innovative strategies leveraging biopolymer engineering and regenerative medicine are proposed as future directives to address the current gaps in managing IUAs. To pave the path toward this endeavour,

we also examined a range of common biomaterials, discussing their physicochemical and mechanical characteristics, latest biomedical applications, and potential limitations, with an emphasis on their roles in tissue engineering and reproductive medicine, particularly in the management of IUAs.

2. Biopolymers Application in Postsurgical Adhesions Management

Although there are several treatment options available for IUAs, issues such as unsuccessful endometrial regeneration, poor reproductive outcomes, and high recurrence rates remain unaddressed medical needs [35]. Nevertheless, bioengineers and material scientists can leverage advanced technologies and innovative approaches to restore fertility and enhance the quality of life among affected patients. These strategies focus on developing, replacing, or regenerating reproductive cells, tissues, and organs using biocompatible and biodegradable materials [50]. The implementation of these innovative strategies offers promising solutions that surpass the complexity and high costs associated with traditional interventions like surgeries and organ transplantation [51]. Despite their therapeutic potential, these innovative health technologies are associated with some translational and regulatory hurdles [52]. Biomaterials can be categorised into four main types based on their intended applications: those used for cell and tissue regeneration, such as scaffolds and hydrogels; for diagnostics, including biosensors and nanoparticles for tumour imaging; for therapeutic purposes, like sutures and wound dressings; and for functional rehabilitation, such as synthetic heart valves [53].

A wide range of biopolymers with biomedical applications has been well characterised but the current research focuses on biopolymers of natural origin such as HA, alginate (ALG), chitosan, collagen, gelatine, fibrin, polylactic acid (PLA), polyglycolic acid (PGA), and carboxymethylcellulose (CMC) [54]. Although biopolymers such as PLA and PGA are commonly used [1] and offer improved biocompatibility and biodegradability, they tend to have higher toxicity and immunogenicity since they differ from the body's natural components [54]. Thus, biopolymers such as HA, gelatine, fibrin, ALG and chitosan are preferred because they replicate essential features of the natural extracellular matrix (ECM), encouraging cellular behaviours like cell adhesiveness, migration, differentiation and proliferation [55].

Failures in the standard clinical management of IUAs using hysteroscopic adhesiolysis prompted researchers to combine hysteroscopic adhesiolysis with clinically relevant biopolymers to prevent adhesions recurrence, maintain endometrial integrity and enhance reproductive outcomes [13,15,42,55]. During the study on combination therapy for the management of IUAs, Mao et al. (2020) reported that among 306 participants (202 in the treatment group and 104 in the control group), those treated with hysteroscopy plus crosslinked HA gel showed greater endometrial thickness (8 ± 1.4 mm vs. 7.5 ± 0.6 mm), higher implantation (18% vs. 10%) and pregnancy rates (26% vs. 15%) [56]. Similarly, a randomised controlled trial (RCT) was conducted to compare HA gel and no treatment in managing IUAs. It was shown that among 82 women in both groups, the HA gel group had a lower rate of IUAs following hysteroscopy (4% versus 11%), and a higher pregnancy rate (61% versus 40%) [43].

Furthermore, a meta-analysis evaluating the effectiveness of HA gel as an adjunct treatment for IUAs in women with a history of miscarriages found that HA gel reduced adhesion scores and significantly enhanced reproductive outcomes in those with moderate-to-severe IUAs. However, no effect of this therapy was observed in women with a mild condition of the disease [57]. Likewise, an RCT was carried out to assess the effectiveness of newly crosslinked hyaluronan (NCH) alone or in combination with an IUD in managing IUAs in 72 women. The results indicated that both treatments improved endometrial

thickness (7.5 mm for the combined treatment versus 6.5 mm for the IUD alone). Also, among the 72 women who later underwent in vitro fertilisation, the pregnancy rates were 27% for the IUD alone, 40% for the IUD plus NCH, and 36% for NCH alone [58].

Among a number of biopolymers, and their biomedical applications reported in the literature [8,58], chitosan, ALG and gelatine-based hydrogels have also been extensively used in biomedicine, notably in eye care, due to high oxygen permeability and lack of irritations leading to inflammatory responses [59,60]. In reproductive biology, these biomaterials are primarily applied in areas such as follicle culture, artificial ovaries, tissue engineering and regeneration, as well as contraception. ALG and its derivatives have been reported to possess biomedical applications, including promoting endometrial regeneration.

An injectable ALG-based zwitterionic hydrogel was designed by combining alginate, glycidyl methacrylate, and the zwitterionic polymer PTSB. This hydrogel demonstrated excellent biocompatibility, biodegradability, and resistance to protein adsorption, all of which contributed to its ability to support angiogenesis, prevent fibrosis, promote endometrial regeneration and restore fertility in tested mouse models [61]. Also, in an RCT, the effectiveness of ALG/CMC/HA (ACH) gel in IUAs after hysteroscopic surgery was compared to CMC/HA (CH) gel, which is recognised as an effective adhesion inhibitor. Four weeks after surgery, the rates of adhesion formation, severity scores, and the type and extent of adhesions were assessed. The results showed that the ACH group had comparable outcomes to the CH group regarding the development of intrauterine adhesions, with no significant difference in adhesion severity [62].

Blending different biopolymers has continuously shown promising results while exploring biomedical applications of various biopolymers. A recent review evaluating the efficacy of a dual-polymer gel composed of CMC and polyethylene oxide (PEO) by analysing the conducted clinical studies in the last 20 years reported that the gel was efficacious in reducing the risk, severity, and extent of postsurgical adhesions. The ability of the CMC+PEO dual-polymer gel to prevent postsurgical adhesions after various types of surgical operations [63] highlights the synergistic potential of the blends from different biopolymers during postsurgical adhesions management.

Another study was conducted to compare the effectiveness of PGA and fibrin–agarose as animal-free scaffolds for growing cells. Endometrial cells grew and proliferated on both scaffolds, and cytokeratin and vimentin expression in seeded cells after 7 days of culturing was detected on both, confirming that fibrin–agarose and PGA scaffolds successfully mimicked the human endometrium [64]. All of the above evidence highlights the importance of combining various types of biopolymers, not only to enhance their physicochemical and mechanical properties but also to boost their therapeutic effectiveness.

Despite the increasing and promising applications of biomaterials, some of them pose potential toxicity risks and involve complex manufacturing processes, necessitating further research and stringent regulation [59]. Furthermore, although natural biomaterials hold significant potential for biomedical applications, many face challenges related to suboptimal mechanical properties, such as gelation time, deformability, and elasticity [65]. To overcome these limitations, chemically modifying natural biomaterials or combining them with synthetic alternatives have been used and offer viable and sustainable solutions [66]. Currently, a number of clinical and non-clinical studies have been conducted to evaluate the safety and effectiveness of biomaterial-based products in preventing adhesions after different surgical procedures. Nevertheless, due to ongoing concerns about the safety and efficacy of some of these materials, continued research and innovation in this field remain essential. Table 4 provides summaries of studies conducted on some biopolymers applied in the management of postsurgical adhesions.

Table 4. Table summarising some studies conducted on biopolymers and their derivatives emphasising efficacy and safety. DF = dosage form.

Biopolymer/Derivatives	DF	Study Context	Study Subjects and Sample Size	Efficacy	Safety	Ref
Hysteroscopic electrosurgical resection plus ACP HA gel vs. hysteroscopic electrosurgical resection alone	Gel	The RCT examined the efficacy and safety of ACP gel in preventing IUAs after hysteroscopic resection and facilitate pregnancy in patients.	In total, 200 patients were recruited and randomised into both treatment and control groups. But, due to dropout, only 164 (82 vs. 82) patients were included in the analysis.	IUAs incidence was lower in the ACP gel group vs. control group (4% vs. 11%, risk ratio = 0.333). Planned pregnancy rate was higher in ACP group vs. control group (61% vs. 40%). Menstrual volume remained same in most cases (86% vs. 89%).	No adverse events were observed during or after gel administration.	[43]
Hysteroscopic adhesiolysis plus ACP HA vs. hysteroscopic adhesiolysis alone	Gel	RCT investigated the short-term safety and effectiveness of HA gels in preventing IUAs after hysteroscopic myomectomy and analysed the characteristics of any IUAs detected during follow-up.	In total, 70 patients who underwent hysteroscopic myomectomy were studied Treatment group received the gel and control group received no treatment after the procedure.	The treatment group which received HA gel had lower IUAs incidence rate compared to the control group with hysteroscopy alone (13% vs. 39%)	Abdominal cramping pain was observed in both groups (21% vs. 26%, respectively). Postoperative vaginal bleeding and/or spotting for more than 7 days observed in treatment and control groups (43% vs. 30%).	[13]
Hysteroscopic adhesiolysis plus ACP HA vs. hysteroscopic adhesiolysis alone	Gel	This RCT aimed to evaluate whether crosslinked HA gel can improve clinical pregnancy rate of patients with moderate-to-severe IUAs after hysteroscopy followed by embryo transfer.	In total, 306 patients were enrolled with 202 assigned to the treatment group and 104 to the control group.	The gel encourages angiogenesis and neovascularisation. Both the clinical pregnancy rate (26% vs. 15%), the implantation rate (18% vs. 10%), and the endometrial thickness on the day of embryo transfer (8 ± 1.4 vs. 7 ± 0.6 mm) were significantly higher in the treatment group compared to the control group.	No adverse effects were detected in both study groups.	[56]

Table 4. *Cont.*

Biopolymer/Derivatives	DF	Study Context	Study Subjects and Sample Size	Efficacy	Safety	Ref
Chitosan-polyvinyl alcohol (PVA)	Hydrogel	The study aimed to develop chitosan-PVA hydrogel designed to prevent abdominal wall adhesions.	Rabbits with injured abdominal walls and cecum were studied.	Assessing the effectiveness of the hydrogel in vivo, all three control cases developed adhesions (one case exhibiting severe adhesion), whereas only one case in the treatment group showed mild adhesion 14 days after hydrogel application. Also, the in vitro study confirmed the hydrogel's anti-inflammatory properties and cytocompatibility.	No adverse effects were detected in the studied rabbits.	[66]
Chitosan plus IUD vs. IUD alone	Hydrogel (Chitosan)	RCT was conducted to compare the efficacy of chitosan-IUD combination with an IUD alone in patients with IUAs who underwent hysteroscopic adhesiolysis.	The study used 303 patients with moderate-to-severe IUAs (American Fertility Society [AFS] score ≥ 5) who underwent hysteroscopic adhesiolysis between January 2018 and December 2020.	A second-look hysteroscopy performed after 3 months revealed that better AFS scores, good menses pattern and endometrial thickness observed in treatment group compared to control group. Also, treatment group showed a significantly higher 1-year clinical pregnancy rate (40%) compared to control group (28%).	No adverse events were detected in the patients.	[67]
Alginate-based zwitterionic hydrogels	Hydrogel	The study aimed to develop an injectable alginate-based zwitterionic hydrogels promoting endometrial repair and restoring fertility.	Rats (female SD rats (220–250 g) were used to establish the endometrial injury model).	Hydrogel promoted cell regeneration and angiogenesis. It suppressed cellular apoptosis and fibrosis. It restored expression of oestrogen/progesterone receptors and endometrial receptivity markers leading to enhanced fertility with pregnancy rate increasing from 67% to 100%.	Cell viability results demonstrated that hydrogel with a relatively high thiol content exhibited lower cytotoxicity, but cell viability of all samples remained above 85%, confirming hydrogel biocompatibility.	[61]

Table 4. *Cont.*

Biopolymer/Derivatives	DF	Study Context	Study Subjects and Sample Size	Efficacy	Safety	Ref
Alginate/CMC/HA vs. CMC/HA	Gel	The RCT was conducted to assess the efficacy and safety of Alginate/CMC/HA (ACP) Compared to CMC/HA (CH) to prevent postoperative IUAs.	In total, 187 patients with a surgically treatable intrauterine lesions (myomas, polyps, septa, IUAs, dysfunctional uterine bleeding) were randomised into two groups of hysteroscopic surgery plus intrauterine application of ACH or CH.	ACH had a comparable efficacy to CH in terms of the adhesion rate and severity. In the case of no baseline IUAs, intrauterine application of ACH after hysteroscopy had a lower rate of IUAs than application of CH ($p = 0.016$).	In total, two patients had diarrhoea and general itching sensation in the ACH group, respectively, and one patient with lower back pain in CH group; but the events were mild, and recovery was spontaneous.	[62]
Autologous platelet gel (APG) vs. chitosan	Gel	This RCT compared the efficacy of APG and medical chitosan in preventing IUAs recurrence after transcervical resection of adhesions.	The study was conducted on 80 females with moderate-to-severe IUAs. Patients were randomised into two groups, APG group ($n = 40$) and chitosan group ($n = 40$).	The IUAs recurrence rate in APG group was significantly lower compared to medical chitosan group (21% vs. 49%). Also, the median AFS score during the second-look hysteroscopy was lower in APG compared to medical chitosan group.	No adverse events were detected in both groups.	[68]
Type I collagen vs. HA-CMC gel	Gel	This was an RCT evaluating the clinical outcomes of using type I collagen gel after therapeutic resectoscopy	In total, 150 women aged > 20 planning to undergo therapeutic resectoscopy were enrolled and randomly assigned to type I collagen group (75 females collagen I vs. 75 females HA-CMC gel).	IUAs' incidence rate was 19% (14/75) and 13% (10/75) in the study and control groups, respectively. At 1 month follow-up, no adhesions were seen in 81% of patients in the study group vs. 87% of patients in the control group. No statistically significant difference between the two treatments was noted.	No statistically significant differences were noted between the two groups in AEs and serious adverse events. Observed adverse events were reproductive system and breast disorders. None of the serious events failed to recover or lead to death.	[69]

Table 4. *Cont.*

Biopolymer/Derivatives	DF	Study Context	Study Subjects and Sample Size	Efficacy	Safety	Ref
PLA scaffold	Nano-scaffolds	The study aimed to evaluate adhesion, growth and differentiation of human umbilical cord stem cells to osteoblast cells on PLA polymeric scaffolds.	Mesenchymal stem cells (MSCs) from human umbilical cord were used.	The scaffold biocompatibility evaluation showed that this scaffold has suitable surface properties for cell growth and proliferation. Flow cytometry demonstrated more than 90% expression of CD105 and CD90 markers (MSCs markers) and no expression of CD45 (hematopoietic marker) on the cell's surface confirming that MSCs can adhere, proliferate and differentiate on PLA scaffold in vitro.	No AEs related to the scaffold were recorded from its interaction with MSCs.	[70]
PLA-PEO-PLA copolymer	Films	The study aimed at providing preliminary design of a new degradable medical device to prevent the formation and recurrence of IUAs.	In vitro evaluation of copolymers was performed in NCTC-Clone 929 cells. In vivo evaluation was performed in rat model of sidewall defect and bowel abrasion. Here copolymers films were compared with Hyalobarrier® (Padova, Italy) group.	The in vitro results revealed that the copolymer (TB77-100-77) had good anti-adhesion, degradation, and swelling properties Also, TB77-100-77 showed a decrease of the incidence of adhesions compared to a commercial anti-adhesion Hyalobarrier® gel Finally, in an ex vivo human uterus, via vaginal route, TB77-100-77 was quickly deployed within the uterus and showed a capacity to adapt to the uterine morphology by spreading over the entire uterine wall.	No AEs were found to be associated with the developed film.	[71]

Table 4. *Cont.*

Biopolymer/Derivatives	DF	Study Context	Study Subjects and Sample Size	Efficacy	Safety	Ref
PGA vs. Fibrin agarose biopolymers	Scaffold	The study aimed at investigating whether PGA could be used as an animal-free scaffold instead of natural fibrin–agarose, which has been used successfully for three-dimensional human endometrial cell culture.	Primary human endometrial epithelial and stromal cells were cultured on fibrin–agarose and PGA polymers.	Endometrial cells grew and proliferated on both scaffolds. Cytokeratin and vimentin expression in seeded cells after 7 days of culture was detected on both, confirming that fibrin–agarose and PGA scaffolds successfully mimicked the human endometrium.	No adverse events were found to be associated with both polymer scaffolds.	[64]

3. Mechanisms of Action for Biopolymers in Managing Adhesions

Fibrosis, a defining feature of IUAs, is a pathological condition characterised by the formation of fibrin fibres between tissues and organs. This occurs due to a disruption in the balance among three key systems: inflammation, angiogenesis, and the blood coagulation process [72]. Biopolymers and biopolymer-based products have been used in the prevention and treatment of IUAs. These novel health technologies can achieve their therapeutic role through various mechanistic pathways. For example, biopolymers, particularly in the form of hydrogels, implants, membrane scaffolds and films, have been used as a primary strategy to prevent direct contact between damaged layers of the endometrium, in addition to facilitating endometrial regeneration and improving reproductive outcomes among women with IUAs [15,42,73]. While preventing damaged endometrial walls from coming together reduces the formation of fibrous cells, resulting in adhesions, improvement of the reproductive outcome was reported to be achieved via increased endometrial thickness, and higher fertilisation, implantation as well as pregnancy rates [42,57].

In regenerative medicine and tissue engineering, the primary goal is to restore tissues lost due to illness, injury, or congenital conditions. Biomaterials have been essential in advancing this field, acting as 3D-printed scaffolds that not only deliver cells but also provide crucial biological signals, structural support, and help recruit the body's own cells to aid in tissue repair [74]. A number of biopolymers, like chitosan and HA, exhibit anti-inflammatory properties that are important for managing IUAs. A hydrogel designed to prevent abdominal wall adhesions was developed by crosslinking chitosan with PVA. Whereas in vitro cell testing showed the hydrogel's anti-inflammatory effects and high biocompatibility, in vivo study using a rabbit model also revealed that the composite exerted an anti-inflammatory effect in the injured cecum and abdominal walls added to demonstrating good biodegradability [64]. Similarly to this, Ma et al. (2021) reported that a lack of antigenicity and toxicity, while demonstrating antibacterial and haemostatic properties, makes chitosan widely applied in tissue engineering [75].

Biological physical barriers, such as amniotic membranes, urinary bladder matrices and platelet-rich plasma, are also common in regenerative and tissue engineering. These were reported to be promising in preventing adhesion formation after various types of hysteroscopic surgical operations. Apart from playing the role of a physical barrier preventing the union of damaged endometrial walls, these scaffolds have diverse therapeutic functions in cell regeneration. For example, epithelial cells of amniotic membranes not only secrete glycoproteins and collagen fibres but also several growth factors such as endothelial growth factors (EGFs), epidermal growth factors (EGFs), keratinocyte growth factors (KGFs), fibroblast growth factors (FGFs) and transforming growth factors (TGFs) in addition to cytokines including angiogenin, dipeptidyl peptidases, interleukin-8 (IL-8) and tumour necrosis factor alpha [76]. Also, these membranes contain amniotic mesenchymal stem cells (MSCs) with pluripotent ability, enabling them to dedifferentiate into endometrial cells [37,76]. This way, they actively contribute to endometrial cells' regeneration after deep injury to the endometrium while modulating immune responses [77]. A systematic review of RCTs comparing various physical barriers for preventing adhesion formation after gynaecological surgery found that the use of Gore-Tex Surgical Membrane, HA, and 4DryField®, Lüneburg (in Germany) yielded the best results. Among these, 4DryField® demonstrated the greatest improvement, with an 85% reduction in adhesion score compared to other biomaterials [78].

Urinary bladder matrices have also been reported to have therapeutic properties in managing adhesions after tissue injuries. An in vivo study showed that following the implantation of these matrices, proliferation and differentiation of endometrial cells were promoted, which gave rise to original tissue formation at the damaged site. A study on

transplanting a urinary bladder matrix (UBM) into the uterine horns of rats with IUAs showed positive results, including endometrial regeneration, thicker endometrial layers, angiogenesis promotion, reduced fibrosis, and improved endometrial receptivity. These outcomes were primarily due to UBM's ability to boost the production of anti-inflammatory cytokines, as well as endometrial receptivity factors like leukaemia inhibitory factor and integrin αVβ3, while lowering proinflammatory cytokines such as tumour necrosis factor α [78,79].

A recent review by DSouza and Amiji (2025) assessed the clinical studies conducted on CMC/PEO gel in managing various types of postsurgical adhesions. It was revealed that the mechanism of action of this gel is based on CMC being responsible for mucosal adhesion and PEO for preventing damaged adjacent walls or organ surfaces from adhering to each other through minimising the deposition of proteins and cytokines onto the surfaces of damaged and adjacent tissues. Then, the gel creates a temporary barrier over injured tissues, reducing contact and fibrosis while supporting normal healing. Nevertheless, since CMC/PEO gel is not metabolised locally, it is cleared from the body through kidney excretion or liver phagocytosis [63].

Equally important, different types of biomaterial-based biomedical devices for managing postoperative adhesions have been approved. These include, Womed Leaf, by Institut des Biomolecules Max Mousseron, Montpellier (France), Seprafilm® developed by Baxter International Inc, Pennsylvania (USA), Interceed®, developed by Ethicon, Somerville, NJ, (USA), Adept®, developed by Baxter, Dearfield, IL, (USA) to name a few [73]. For example, the conducted nonclinical study comparing Womed Leaf and HA gel in managing IUAs in rat models showed that Womed Leaf could not negatively affect endometrial thickness or reproductive outcomes. Similarly, the in vivo study to evaluate the safety and efficacy of Womed Leaf in women who underwent hysteroscopic resection of myomas confirmed that the implant did not induce irritations or cervical trauma and efficiently showed potential to prevent IUAs formation among 20 out of 23 treated women by physically separating the endometrial walls [80,81].

4. Engineering Methods for Biopolymers with Biomedical Applications

The growing need for advanced health technologies, driven by the increasing complexity of human diseases such as female reproductive disorders, has significantly accelerated advancements in material science and regenerative medicine. In this regard, innovative processing techniques have emerged to improve the performance of clinically relevant biomaterials, while ensuring their adherence to safety and efficacy requirements for better patient outcomes. Currently, several cutting-edge engineering approaches are commonly utilised in the design of biopolymers and their derivatives for biomedical use, particularly in managing IUAs.

Several processing techniques have been applied to produce biomaterial products for managing postsurgical adhesions and endometrial regeneration. These may include hot melt extrusion (HME), electrospinning, and 3D printing, also known as additive manufacturing (AM). These techniques contribute to the production of various products including hydrogels, drug and growth factor delivery systems, membrane-encapsulated cells, biomaterial scaffold, composite biopolymers, as well as the most recent smart or responsive biopolymers [16,82,83]. However, given the physiological environment of the uterus, these biomaterials should meet some requirements in order to fulfil their therapeutic functions. Biomaterials with biomedical application in the uterus should (1) be easy to administer, such as via injection or minimally invasive procedures, (2) have biological functions to promote endometrial regeneration, (3) access the injury site and prevent fibrosis [83] and, most importantly, (4) respond to varying shapes and sizes of uteri.

A number of studies have reported on the application of some of these technologies in tissue engineering and regeneration. Hydrogels have extensively been reported to help in managing IUAs pre- or postsurgical operations. Various natural biopolymers, such as HA, ALG, collagen, chitosan, and gelatine to name a few, have been produced in hydrogel dosage forms and showed therapeutic potential in wound healing and cell regeneration after various injuries [84–86]. Also, collagen-based biomaterial products, such as collagen hydrogel and decellularised extracellular matrix (ECM), have significantly contributed to the development of engineered reproductive tissues [34]. For example, telomerase-immortalized human endometrial stromal cells were embedded in a collagen I hydrogel and exposed to hormones in vitro. The findings indicated that the engineered endometrial stroma could replicate the natural structural and biochemical morphologies that take place during the secretory and menstrual phases of the menstrual cycle [87]. However, limitations related to limited hydrogel stability were reported as a hindering factor to the developed products. Chemical modification and blending of these materials with others have been reported to be useful in improving the hydrogels from these biomaterials [87–90].

Hormone delivery systems have been used to improve the therapeutic effects in IUAs treatment mainly due to poor hormone solubility. While studying the safety and efficacy of oestrogen-releasing intrauterine stents, it was discovered that the reduction in adhesions was significantly greater in the treatment study subjects compared to the control group (93% versus 58%), and the endometrium in the treatment group was thicker than that in the control group [91]. Also, the administration of MSCs such as intravenous injection was shown to face certain challenges, notably low retention rates and limited therapeutic outcomes [45]. However, stem cells combined with delivery systems were reported to improve their retention at the active site which boosts their therapeutic effects on IUAs [43,91]. A recent study revealed that the minimally invasive injection of MSCs combined with Matrigel microspheres directly into the rat endometrium was a safe and effective technique which resulted in increased endometrial thickness and neovascularisation, as well as an improved fertility rate from 25% in impaired to 75% in regenerated endometrium [45].

Similarly, in a murine model of uterine injury, it was discovered that combining endometrial stromal cells with HA hydrogel significantly reduced fibrosis and promoted endometrial regeneration. This effect was demonstrated by the expression and secretion of key implantation biomarkers, including Desmin, CD44, PECAM, and IGF-1, and live birth was found in all subjects with regenerated endometrium [44].

Furthermore, researchers studied the effect of a poly (glycerol sebacate) (PGS) scaffold loaded with bone marrow stromal cells (BMSCs) to prevent IUAs and compared its regenerative potential for damaged endometrium with poly (lactic-co-glycolic acid) (PLGA) and collagen scaffolds in a rat model. Unlike direct BMSC injections, PLGA and collagen scaffolds, the PGS scaffold prolonged the residence time of BMSCs in the uterus. The latter helped restore the endometrium and achieved an implantation rate of $72 \pm 6\%$ that was the same as that of collagen/BMSCs, but higher than one in the PLGA/BMSCs scaffold [92].

The collagen membrane scaffold was successfully developed and proven to support the attachment and movement of BMSCs. After being implanted into an injured uterus, it increased stem cell presence at the site and boosted the release of vital growth factors like fibroblast growth factor (bFGF), transforming growth factor-β1 (TGF-β1), insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor (VEGF). As a result, it promoted cell growth, improved blood vessel formation, and restored the endometrium's ability to support implantation [93]. These underscore the critical role of biomaterial scaffolds as effective and safe delivery systems of stem cells and other therapies.

Additive manufacturing, also known as 3D printing, is an innovative processing technology that facilitates material deposition in a layer-by-layer approach to fabricate pre-defined 3D complex structures [16]. This processing method has enabled the creation of nanomaterials which are like in vivo ECM and have excellent porosity. These may include nanofibres, nanosheets, and nanotubes that have shown clinical potential in endometrial regeneration. For instance, nanofibres derived from chorionic villi have been found to mimic the ECM environment of MSCs and facilitate the production of abundant exosomes. When these exosomes were encapsulated within the chorionic villi nanofibres, they significantly enhanced endometrial repair and improved reproductive outcomes [94]. Likewise, a nanofibre created from decellularised pig skin ECM demonstrated the ability to adhere to the endometrial lining, release bioactive growth factors, and efficiently recruited endogenous cells to the site of the injury. This nanofibre also helped minimise fibrosis and significantly enhanced fertility in a rat model of endometrial injury [95].

By leveraging HME, electrospinning, and 3D-printing techniques, researchers developed an electrospun scaffold from PGA to culture bovine endometrial epithelial and stromal cells. The study revealed that the scaffold's structural design closely resembled natural tissue, supported fibronectin deposition, and exhibited proper expression of vimentin and cytokeratin. These results suggest that the scaffold is a promising tool for investigating endometrial pathophysiology [96]. Also, using 3D extrusion-based bioprinting, researchers developed a bilayer endometrial construct made from a sodium ALG-HA hydrogel, with endometrial epithelial cells incorporated into the upper layer. In a rat model, this construct successfully regenerated the endometrium's structure and morphology, and notably improved reproductive outcomes following implantation, among 12 out of 16 rats as compared with 2 out of 16 in the control group. This reveals the clinical potential of 3D-printing technology in the effective management of IUAs following endometrial injuries.

The concept of 4D printing has also emerged as a groundbreaking technology driving the advancement of smart materials for biomedical use. This innovative approach is designed to tackle a variety of health-related challenges by creating intelligent materials that can dynamically respond to external cues, such as temperature, pH, light, and magnetic fields, by changing colour, shape or size. These adaptive properties have enabled their use in diverse applications in medical and pharmaceutical industries, including drug delivery systems, tissue engineering, biosensors, and medical device development. However, despite their therapeutic potential, challenges such as limited biocompatibility, stability, and scalability of smart materials still need to be addressed [97]. For example, a thermoresponsive hydrogel implant to prevent IUAs was developed by combining recombinant type III collagen with Pluronic HP407/HP188 excipients. The results in a rat model showed biocompatibility, promotion of endometrial regeneration, anti-fibrotic potential in addition to promoting angiogenesis [98].

Since this innovation provides adaptability and dynamic responsiveness across structures and systems of varying scales, it opens new opportunities for integrating programmability and precise decision-making capabilities [99]. In the treatment of IUAs, smart materials may have significant advantages, especially in overcoming the limitations of some current therapies such as physical barriers that have failed to accommodate the diverse shapes and sizes of uteri. The adoption and wide application of this advancement can pave the way toward more precise and personalised approaches in managing reproductive disorders, particularly IUAs.

Recent advancements have also focused on organ-on-chip technology to better understand disease mechanisms and evaluate potential drug treatments [100]. In this context, endometrial organoids have been generated using hydrogels combined with peptides

and MSCs to closely mimic the natural endometrial environment. These organoids not only help stimulate internal tissue regeneration but also offer valuable insights into the pathophysiology and mechanisms behind endometrial repair. Although some studies have reported on the potential of organoid transplantation, this technology remains relatively underexplored in reproductive medicine [100,101]. Nevertheless, it holds great promise for overcoming limitations in clinical research, such as the heavy reliance on animal models and species-specific differences, potentially paving the way for standardised models of endometrial regeneration [102]. Ongoing research and innovation of this technology are highly recommendable, since it has the potential not only to understand disease mechanisms and novel drug effects but also promote sustainability and improve the well-being of humans, animals, and the environment.

5. Examples of Naturally Occurring Biopolymers and Their Applications

This section explores various naturally occurring biomaterials and their roles in biomedical applications. It emphasises their essential chemical, physical, mechanical, and biological properties that contribute to their functionality. Despite the increasing use of biomaterial-based products in the biomedical field, several challenges still limit their full potential [102,103]. As such, this review also examines common obstacles, such as physical, chemical, regulatory, and translational issues, faced by these materials, recent advancements aimed at overcoming them, and remaining gaps. More details on these limitations were provided in Section 6 of the manuscript.

5.1. Hyaluronic Acid

HA, also known as hyaluronan, is an anionic and non-sulphated naturally occurring biopolymer that falls within the category of mucopolysaccharides, also known as glycosaminoglycans [50,53]. Its chemical structure comprises a long linear chain of two disaccharide repeating units, namely d-glucuronic acid and N-acetylglucosamine, linked by alternating β-(1–4) and β-(1–3) glycosidic bonds [54]. This biopolymer is found in all vertebrate connective tissues and throughout the human body, especially in synovial fluid, the umbilical cord, urine, and the ECM. It plays a crucial role in cellular processes like cell proliferation, migration, and differentiation [4,104], in addition to exhibiting anti-inflammatory and immunosuppressive properties [38]. In vertebrates, three genes, namely Has1, Has2, and Has3, are responsible for HA synthesis, whereas in bacteria HA synthesis is enabled by the expression of HasA, HasB, and HasC genes [105,106]. Although *Streptococcus species* naturally produce large quantities of HA, this source is unsuitable for humans and other vertebrates due to the high endotoxin levels of these bacteria [107]. Hence, *Lactobacillus lactis* has been biotechnologically engineered as a safer alternative for HA production [4].

HA maintains its optimal stability at neutral pH and 40 °C but deteriorates rapidly when exposed to acidic or alkaline environments [108]. The molecular weights (MWs) of HA vary depending on its source. For example, in the human body, the MWs of HA range from 10^3 to 10^7 Da in both the serum and vitreous humour of the eye, respectively. It has also been reported that the different chemical structure forms and MWs of HA are directly linked to its distinct properties and often-contrasting physiological functions [46,108,109]. Typically, short and medium HA molecules exhibit immunostimulant, proangiogenic, and antiapoptotic properties, while longer polymers are associated with immunosuppressive and antiangiogenic effects [110]. However, in another review, it was reported that HA with high MWs exhibits anti-inflammatory properties by regulating the recruitment of inflammatory cells, while low MWs of HA tends to be pro-inflammatory, encouraging angiogenesis and tissue remodelling during wound healing [110]. These may partly ex-

plain the reason why this biopolymer has a diverse range of physiological roles in the body. Considering these observations, precautions should be taken when selecting HA to be used for biomedical applications. Similarly, HA can be in linear (non-crosslinked) or crosslinked forms. Several reports revealed that once in non-crosslinked form, it is exposed to enzymatic degradation compared to crosslinked forms. Thus, as previously discussed, in tissue engineering, particularly during IUAs management, the application of crosslinked HA hydrogels after hysteroscopic resection of adhesions has revealed promising outcomes [13,42,55].

The physicochemical and biological properties of HA, including viscoelasticity, hydrophilicity, biocompatibility, biodegradability, non-toxicity, and non-immunogenicity, make HA-based preparations suitable for a range of biomedical applications [104,108]. Structurally, HA helps maintain the gel-like nature and stability of the ECM by interacting with various ECM proteoglycans, such as aggrecans [111]. This biopolymer is extremely hydrophilic, with each HA chain containing a carboxyl group that dissociates at physiological pH, making it a polyanionic molecule. Consequently, HA demonstrates remarkable water-retention capacity, capable of holding up to 1000 times its own volume in water. This property significantly influences its rheological and elastic behaviour, as well as key biological functions like enhancing wound healing and supporting cell lubrication [3]. These properties are critical in the management of IUAs which are characterised by tissue fibrosis inside the uterus. HA is essential for cell-to-cell communication, one of the vital processes for maintaining human body homeostasis. To achieve this, HA has the well-known and characterised membrane glycoprotein receptor called 'CD44' to which it attaches, forms a pericellular coat around cells, and interacts with cell membrane proteins to regulate key physiological processes, such as cell adhesion, migration, and proliferation [46,87].

HA plays a vital role in managing IUAs and addressing the rising global issue of female infertility. Numerous recent clinical trials have shown that HA gel supports endometrial regeneration after intrauterine surgeries, encourages angiogenesis and neovascularisation and, most significantly, enhances reproductive outcomes [13,42,55,57,111,112]. Additionally, as previously noted, in a murine model, it was demonstrated that functionalised endometrial stromal cells with HA/fibrin composite hydrogel effectively reduced fibrosis, promoted endometrial regeneration, and improved reproductive outcomes. This was achieved by enhancing the expression of implantation biomarkers, including Desmin, CD44, PECAM, and IGF-1 [44]. During a review on advances in nanomedicine and biomaterial for endometrial regeneration, it was reported that encapsulating stromal cells on the biomaterial composite not only serves to prevent cell loss during uterine injection but also ensure an adequate number of cells remain in the uterus to support endometrial regeneration. This ultimately translate into an improved endometrial receptivity and reproductive outcome [103] while addressing the issue raised for the conventional treatments which do not aim at restoring reproductive outcomes [113].

The application of crosslinked HA hydrogel for the prevention of IUAs after a hysteroscopic myomectomy was investigated. The research findings showed a reduction in the incidence and severity of IUAs, and discovered the potential of synergistic effects of hysteroscopic myomectomy and HA hydrogels among women undergoing hysteroscopy [13]. Several HA-based implants, such as Hyalobarrier Gel Endo®, by Anika therapeutics, INC. in Padova (Italy), and Intercoat® Nordic Pharma, Paris, (France), have been developed to prevent IUAs. While a Belgian consensus on adhesion prevention noted their potential benefits, their effectiveness is minimal in terms of adhesion prevention and reproductive outcome, and these products were not eligible for reimbursement [114]. The shortcomings of commonly used barrier methods in preventing IUAs may be linked to prior research emphasising uterine anatomical restoration over endometrial stem cell func-

tionality. HA-based membranes, device-loaded with oestrogen and growth factors, have been recommended to promote cell regeneration. However, as noted earlier, prolonged oestrogen use is not advisable due to reported adverse effects and may compromise the device's effectiveness [115].

5.2. Alginate

ALG is a polyanionic and water-soluble polysaccharide [116], the second-most-abundant natural polymer, which is primarily extracted from brown seaweed species [116,117]. ALG is a polysaccharide made up of linear α-L-guluronic acid (G-blocks) and somewhat more branched β-D-mannuronic acid (M-blocks) copolymers. These blocks are connected by (1,4)-glycosidic bonds and can form gels when hydrated [118]. ALG's superior degradation profile makes it particularly well-suited for drug delivery applications. It has thickening, gel-forming, and stabilising properties, and high-water retention capacity. ALG forms acid gels at low pH and these gels are stable at temperatures ranging from 0 to 100 °C [119]. As a result, it is commonly used as a therapeutic delivery system and an excipient in controlled-release drugs [118,119].

ALG is renowned for its exceptional properties, including biocompatibility, biodegradability, mechanical properties, bioresorption ability, and low cost, making it highly suitable for a wide range of biomedical applications [116,120,121]. The medical application of ALG in wounds, scars, and bone injury healing, cell regeneration, and scaffolding for cell growth, and in drug delivery systems have been reported [58,60,61,117]. ALG-based hydrogels have numerous biomedical uses and are common in pharmaceutical and medical device industries. Scaffolds created from ALG act as frameworks that support cell growth and mimic the physical and chemical characteristics of the natural ECM [118]. ALG has also been proven effective for encapsulating isolated follicles in in vitro culture and for developing artificial ovaries. Moreover, ALG-based hydrogels have demonstrated their ability to replicate the natural microenvironment prior to ovary cryopreservation [122], highlighting their potential in addressing female infertility issues. However, this biomaterial showed enhanced therapeutic effects when used in combination with others.

An IUD composed of ALG combined with Matrigel and poly (lactic-co-glycolic acid) (PLGA) exhibited improved properties, enhancing its effectiveness in the manufacture of artificial ovaries [59,116]. Also, a study on the development of a biodegradable artificial ovary showed that an ALG–Matrigel matrix was able to facilitate ovarian cell proliferation and, after ovarian cells grafting, the matrix degraded effectively while allowing angiogenesis and showing minimal inflammatory responses [60]. A porous scaffold composed of ALG, and gelatine was designed to address IUAs. Testing both in vitro using human hepatocarcinoma cell lines and in vivo in rat models revealed that the scaffold demonstrated excellent compatibility and effectively promoted endometrial repair while preventing adhesions, respectively [123].

An injectable ALG-based zwitterionic hydrogel was developed and tested to evaluate its effect to endometrial regeneration and fertility restoration in rat models. ALG-based zwitterionic hydrogels have been shown to support cell regeneration and promote angiogenesis, aiding in the recovery of epithelial cells, glands, and cell proliferation. These hydrogels also reduced cell death and collagen buildup, which significantly decreased the formation of adhesions. Their ability to restore the expression of oestrogen and progesterone receptors, along with endometrial receptivity markers, such as VGEFA, integrin and alpha and beta tubulin, played a key role in improving embryo implantation and fertility, resulting in an increase in pregnancy rates from 67% to 100% in the treated rats [61].

However, due to certain limitations associated with ALG, additional research is needed to develop new processing methods that can tailor the physical and chemical properties

of ALG and its derivatives to meet specific clinical needs. For instance, It was highlighted that aligning the stiffness of the ALG-based scaffold with that of the surrounding tissue and fine-tuning its degradation rate can help ensure that infiltrating cells stay viable, retain their intended phenotype, and effectively direct their activity throughout the entire wound healing process [118].

5.3. Chitosan

Chitosan, a natural cationic polysaccharide, is typically derived from the shells of crustaceans such as shrimp, crab and lobster. Chitosan is a linear polysaccharide composed of glucosamine and N-acetylglucosamine units linked by β (1–4) glycosidic bonds. Its various forms arise primarily from differences in the degree of deacetylation and molecular weights, which range from 300 to 1000 kDa [123,124]. As a cationic biopolymer, chitosan can readily interact with anionic biological molecules, like heparin and heparan sulphate, influencing the activity of various cytokines and growth factors crucial for tissue regeneration. In addition to being a biodegradable biopolymer, chitosan has a hydrophilic surface that confers it the capacity to promote cell adhesion and proliferation, and its degradation by-products are not toxic which render it medically relevant [125,126].

Chitosan is synthesised through either chemical or enzymatic processes. The chemical method, widely used for chitosan synthesis, involves an acetylation reaction where acetyl groups are removed from N-acetylglucosamine to generate D-glucosamine, which increases chitosan's solubility in water. This reaction must take place in a heterogeneous phase, using sodium or potassium hydroxide in an inert atmosphere to prevent depolymerisation. Alternatively, biosynthesis using chitinases offers a different acetylation route for chitosan production from chitin and is currently being utilised [126]. Chitosan contains reactive primary amines as well as primary and secondary hydroxyl groups, which provide flexibility for chemical modifications. These modifications can enhance its physicochemical and biological properties, making it suitable for a wide range of biomedical applications [127].

Chitosan has been recognised as a safe material for use in food, cosmetics, and medical devices in several countries, including Finland, the USA, Italy, and Japan [128]. Several studies assessing the safety of chitosan have shown that this biomaterial causes no side effects in the study subjects [128,129]. In addition to being considered a safe biomaterial for pharmaceutical and biomedical applications, chitosan is also recognised for its cost-effectiveness, biodegradability, biocompatibility, hydrophilicity, nontoxicity, high bioavailability, amenability to modifications, affinity to proteins and high films and gel-forming capacity [4,130]. Thus, a variety of chitosan-based therapeutic biomaterials have been developed for diverse biomedical applications, such as treating cancer, immune disorders, microbial infections, hypertension, inflammatory conditions, coagulation disorders, high cholesterol, diabetes, drug/gene delivery systems, wound dressing, tissue engineering and cell encapsulation [130–132].

Additionally, its excellent water retention and swelling properties boost porosity and surface area, which are vital for cell adhesion and tissue regeneration [124]. Correspondingly, chitosan demonstrated enhanced therapeutic effects when used in combination with HA. Leveraging their common antimicrobial, antioxidant, and anti-inflammatory properties, researchers have combined chitosan and HA to enhance skin care. This synergistic approach has led to improved health outcomes, particularly in tissue regeneration and wound healing [125]. Medical chitosan has been shown to mitigate the sequelae of abdominal, fallopian tube, and other hysteroscopic surgeries, including preventing adhesion formation and recurrence. It achieves this by promoting fibrocyte growth while preventing fibrosis [37,133]. In addition, this biopolymer uniquely supports local haemostasis and prevents bacterial growth with its lubricant properties, along with its physical barrier function,

biodegradability, and resorbability. It has been suggested that combining medical chitosan with oestrogen therapy could work synergistically to enhance endometrial regeneration and prevent adhesion recurrence after hysteroscopic adhesiolysis [38].

5.4. Collagen

Collagen is the most prevalent structural protein in mammals and aquatic organisms, playing a vital role in the formation of the ECM and basement membrane structures [55]. It is widely known for its outstanding structural strength and versatility. It plays a vital role in maintaining the durability, flexibility, and connectivity of various parts of the body [134]. Collagen is characterised by its triple helix structure, where tightly coiled amino acid chains provide exceptional tensile strength [135]. This polymeric biomaterial has a wide range of biomedical applications, and several collagen-based products are currently on market under the form of solutions, hydrogels, powders, sponges, scaffolds, as well as thin films. The biomedical application of collagen is primarily owed to its inherent characteristics, including excellent biocompatibility, bioresorbability, non-toxicity, non-antigenicity, adhesiveness, and strong tissue integration ability. Furthermore, its high flexibility, tensile strength, and mechanical properties make it adaptable to modifications that enhance its biomedical performance [115,135].

Collagen is recognised for its capacity to self-assemble into a three-dimensional fibre network, enhancing its mechanical strength, which is an essential requirement for building tissue scaffolds. Additionally, this biomaterial can bind to cell surface receptors, promoting robust cell adhesion, growth, and migration, all of which are vital for the healing and tissue regeneration process [135,136]. The wide range of biomedical applications for collagen also stems from the variety of its types, each with unique structures and characteristics. In total, the collagen superfamily is made of 28 types of collagen, each localised to specific tissues and serving distinct functions in the body [136–138]. Of these, the five most cited in the literature are types I, II, III, IV, and V [35,135,139]. In terms of abundance of collagen in the body, contradictory reports are encountered in the literature. Although Lin and Brodsky (2016) identified that type I collagen as the most abundant and widely used in biomedical applications, another review focusing on the main and minor collagen types in articular cartilage reported that types II, IX, and XI are the most prevalent in the body [138]. Collagen is also noted for its elasticity, an ability to regain its original shape after being stretched or deformed, an important property that helps cells withstand mechanical stress and strain [136].

A variety of hydrogels including collagen-based hydrogels have shown encouraging results in tissue engineering and reproductive medicine. Collagen can act as a signalling molecule, impacting cell behaviour, tissue development, and wound healing [135]. ECM-derived hydrogels are highly recommended due to preclinical trial findings demonstrating their ability to closely replicate the natural microenvironment, exhibit excellent biocompatibility, and deliver superior clinical outcomes [122]. The literature reveals numerous studies investigating the biomedical applications of collagen in the field of reproductive medicine, particularly using animal models. Collagen has been reported to successfully deliver stem cells and growth factors in murine models of IUAs, premature ovarian failure, and vaginal atrophy [59,121,140]. This biomaterial also has additional advantages in various areas of biomedicine, including dental surgery, drug delivery, and cardiology. For instance, collagen in dental implants aids in the integration of the implants and supports the regeneration of periodontal tissue. It also enables controlled drug release within implants, promoting localised and extended drug delivery. Additionally, collagen-based materials are reported to be useful in the creation of vascular grafts and heart valve prostheses [134].

Another study was carried out to assess the impact of a sodium ALG hydrogel combined with type III recombinant collagen (rCoIII) and MSCs on regenerating the endometrium and restoring fertility in rat models with a thin endometrium. The results demonstrated that this composite effectively stimulated endometrial repair and improved fertility in the treated animals. Additionally, the therapeutic benefits were attributed to the MSCs' ability to influence the mesenchymal–epithelial transition of endometrial stromal cells. These outcomes underscore the promising clinical potential of using an Alg-rCoIII hydrogel in conjunction with MSCs for enhancing endometrial regeneration [141].

A hydrogel implants to prevent IUAs was developed by combining recombinant type III collagen with Pluronic HP407/HP188 excipients. When injected into the uterine cavity, the hydrogel transitioned from a sol–gel to a gel in response to body temperature, ensuring targeted delivery and sustained treatment. In vitro studies showed the implant's good biocompatibility, promotion of endometrial cell regeneration, suppression of fibrotic factor gene expression (TGF-β1), and stimulation of angiogenesis. Additionally, the in vivo experiments in female rats demonstrated that the implant improved retention at the injury site, enhanced endometrial regeneration, increased blood supply, and reduced abnormal fibrin deposition [98].

This suggests that this hydrogel can effectively prevent postsurgical intrauterine operations, highlighting their clinical potential as a promising adhesion prevention strategy in managing IUAs. A recent clinical study evaluating the effectiveness of type I collagen gel compared to HA-CMC hydrogel following therapeutic resectoscopy also found that both treatments successfully prevented adhesion formation, with no adverse events observed in the participants [70]. Considering the diverse types of collagens and their promising therapeutic potential, continued research on this naturally occurring biomaterial is strongly encouraged, as it could lead to the discovery of new biomedical applications and help drive innovation in healthcare.

5.5. Gelatine

Gelatine is a biomaterial derived from the partial breakdown of collagen. It is extracted from the bones, skin, and connective tissues of animals such as cattle, horses, pigs, chickens, and fish [51]. It is readily sourced from natural resources, offers great stability, and can modify drug release patterns. This latter quality implies that gelatine can control drug release dynamics, effectively delaying the release of a drug until it reaches the intended target site [135]. This property allows for more precise and controlled delivery, improving the therapeutic efficacy and minimising potential side effects by preventing premature drug release. Gelatine is recognised for its notable qualities, including excellent gelation, biocompatibility, and biodegradability [103].

Gelatine has known potential applications in various areas including drug delivery, scaffolds for tissue regeneration, and wound dressings [134]. In tissue engineering, gelatine-based scaffolds serve as a supportive 3D structure that promotes cell adhesion, growth, and tissue regeneration. However, to counteract its inherent limitations, enhance its properties, and optimise its uses, gelatine has been combined with other materials through chemical modifications. For example, incorporating PVA into gelatine increased the gelling temperature of the composites from 41 °C to 80 °C. Additionally, the tensile strength and elongation at break improved from 2.89 MPa to 3.40 MPa and from 342% to 367%, respectively [142]. By utilising electrospinning and the self-assembly process, highly porous, 3D nanofibre scaffolds were created via crosslinking PCL and gelatine with a genipin crosslinker. The resulting polymer scaffold resembled the nanofibrous structure of endogenous ECM and demonstrated strong mechanical strength, biocompatibility, as well as promoting the proliferation and adhesion of dermal fibroblast cells [143].

Embryonic stem cells from early blastocysts are capable of self-renewal in undifferentiated state and differentiating into all types of adult cells. Yet, sustaining them long-term has been challenging in its clinical applications. To overcome this, research has demonstrated that gelatine-based, structurally dynamic hydrogels, which mimic the natural dynamics of the ECM, can support clonal expansion and enhance cell viability more effectively than covalently crosslinked gelatine hydrogels with similar stiffness and biodegradability [86].

5.6. Fibrin

Fibrin is a key blood component essential for blood clot formation and wound healing. As a protein polymer, it also contributes to thrombosis and other pathological processes related to the ECM. Its notable mechanical and rheological properties enable effective interactions at both molecular and cellular levels. Fibrin is known for its high viscosity, elasticity, structural stability, and adaptability to modifications [102,144]. Unlike many other polymers, fibrin demonstrates remarkable stiffness, particularly when subjected to shear forces, tension, or compression, an attribute linked to its intricate, multi-scale hierarchical structure. It was reported that, except for bone and fibrocartilage, the stiffness of fibrin is comparable to that of most human tissue where, for example, the elastic modulus of fibrin (1 kPa) is not different from that of platelet-rich fibrin. Although these properties are crucial for its biomedical applications, the complete range of fibrin's biological functions remains not fully understood [145].

Recent advancements leveraging the clinical potential of fibrin are based on its critical role in blood clotting mechanisms and wound healing processes. Normally, after tissue or vascular injury in the body, the soluble protein fibrinogen is enzymatically transformed by a serine protease called thrombin into insoluble fibrin. Fibrin forms a structural scaffold that binds platelets and red blood cells, facilitating clot formation, a key step in normal wound repair and subsequent tissue regeneration. Fibrin can be degraded through a process known as fibrinolysis, which is controlled by the enzyme plasmin or by the activation of metalloproteinases. The latter involves proteolytic and esterolytic reactions that lead to the remodelling of the ECM, while also acting as a negative feedback mechanism to regulate matrix degradation [103,146]. Fibrinogen, a 340 kDa homodimeric protein produced by liver hepatocytes, serves as a precursor to fibrin and has a lifespan of approximately four days. Once secreted, it enters the bloodstream, where elevated levels have been linked to various inflammatory conditions [103,146,147]. Given that IUAs are also marked by significant inflammation, fibrin or fibrinogen may offer therapeutic potential in treating this condition.

Due to its inherent properties, discussed above, fibrin has attracted research interest as a potential therapeutic biomaterial for promoting endometrial regeneration following IUAs. Platelet-rich fibrin (PRF), derived through the standard centrifugation process of whole blood, has recently been shown to offer various clinical benefits. These range from enhancing blood coagulation to serving as a supportive scaffold for tissue regeneration, while also preserving growth factors and stem cells [148].

The increasing demand for the regeneration of damaged cells, tissues, or organs has driven ongoing advancements in biomaterials research. Various scaffolds have shown encouraging outcomes, particularly in managing postsurgical adhesions. Among them, fibrin scaffolds are well recognised for their outstanding biological properties, making them highly suitable for biomedical use. In addition to the previously discussed rheological and mechanical properties, fibrin's biological properties include haemostatic ability, excellent biocompatibility, and a favourable biodegradation profile, which make it one of the most promising biomaterials in biomedicine. In biomedical applications, such as wound healing and tissue regeneration, fibrin scaffolds function as an initial matrix that supports cell

migration, differentiation, proliferation, and adhesion, while also playing a vital role in cell–matrix interactions [144].

Several studies have investigated the potential of fibrin, fibrinogen, and their derivatives in managing IUAs and enhancing female fertility. One such study specifically examined the effects of platelet-rich fibrin (PRF) on endometrial regeneration in a rat model. The results revealed that PRF exudates stimulated the proliferation and migration of endometrial stromal cells in vitro. Furthermore, when transplanted into rat uteri, PRF helped preserve uterine structure, supported the regeneration of the endometrial luminal epithelium and glands, and significantly reduced adhesion formation [149]. Also, fibrin combined with HA as a polymer composite has been studied in a murine model with an injured endometrium. As reported earlier, the results showed that this composite helped prevent fibrosis, promote endometrial regeneration, and enhance reproductive outcomes [39].

Another study developed a stable nanofibre scaffold composed of fibrinogen and P(LLA-CL) using electrospinning, which was tested in rat models. The results showed that the scaffold significantly improved endometrial regeneration after injury by increasing endometrial thickness, angiogenesis, and gland formation, while reducing fibrosis. Additionally, it downregulated the expression of TGF-β1, a key cytokine involved in adhesion formation, during the early injury phase. Fertility tests demonstrated improved pregnancy rates in treated rats, and safety evaluations revealed no adverse effects on major organs, indicating the scaffold's potential as a safe and effective treatment for IUAs and fertility restoration [150].

In assessing the effectiveness of PGA and fibrin agarose as animal-free scaffolds for three-dimensional human endometrial cell cultures, it was observed that endometrial cells grew and proliferated well on both scaffolds. Additionally, the expression of cytokeratin and vimentin biomarkers in the seeded cells after 7 days of culturing on both scaffolds confirmed that both fibrin–agarose and PGA scaffolds successfully replicated the human endometrium [64]. This suggests that these biomaterials could serve as promising candidates for developing potential health technologies aimed at treating pathophysiological conditions affecting the human endometrium.

The effectiveness of fibrin and its derivatives has been investigated. In an RCT, researchers evaluated the use of a collagen–fibrin sealant patch as an adjunct treatment during inguinofemoral lymphadenectomy for vulvar cancer. In this study, the inguinofemoral regions were randomised; one side received the collagen–fibrin patch, while the other underwent standard closure without the patch. After a six-month follow-up, the incidence of lymphedema was 44% in the treatment group and 50% in the control group. The findings indicated that the collagen–fibrin sealant patch did not significantly reduce postoperative lymphorrhagia or lower the rate of postoperative complications in patients undergoing the procedure [151]. A 10-year systematic review assessing the efficacy and safety of fibrin glue in patients undergoing extraperitoneal inguinal hernia repair reported that, out of 703 participants, 96% were either satisfied or very satisfied with their outcomes six weeks post-surgery and the hernia recurrence rate was just 1%. These findings indicate that fibrin glue is highly safe and dependable, offering a high level of patient satisfaction and a low risk of chronic pain development [152]. Although fibrin has shown promising potential in biomedical applications, particularly in in vitro and animal models, additional clinical research is necessary to ensure its safety and effectiveness in humans, and to support its successful translation into clinical use.

5.7. Polylactic Acid

Polylactic acid (PLA) is an aliphatic, environmentally friendly biopolymer with various biomedical applications, largely due to its thermoplasticity, excellent processability, me-

chanical strength, biodegradability, bioresorbability and biocompatibility properties [153]. This biomaterial is well recognised for being cost-effective, dimensionally stable, and rigid [154]. PLA is produced through the polymerisation of lactic acid (LA), a naturally occurring organic acid produced through the sugar fermentation process. Figure 2 illustrates the structural formula of PLA. LA exists in two enantiomeric forms: L- and D-LA. Consequently, PLA can exist as pure poly-L-LA (PLLA), pure poly-D-LA (PDLA) and a mixed form of poly-D, L-LA (PDLLA) [1,153]. PLA with over 90 percent PLLA content tends to be crystalline. As the amount of PLLA decreases, both the melting and glass transition temperatures of PLA also decrease. These temperature values are vital for predicting the polymer's physical, chemical, and biological properties. Whereas PLA glass transition temperature ranges between 45 and 65 °C, its melting point varies between 150 and 162 °C [154,155]. Also, the melting point of semi-crystalline PLLA ranges from 170 to 180 °C, but when blended with PDLA, the melting temperature increases to 220–230 °C, enhancing its thermostability [153].

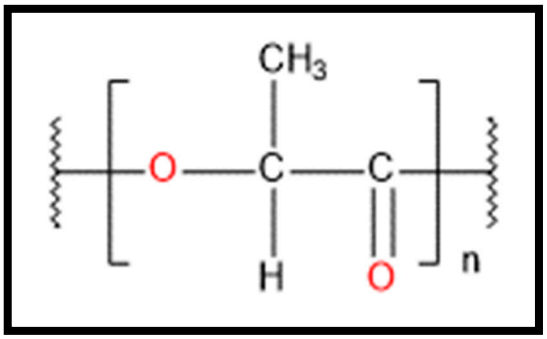


Figure 2. Structural formula of PLA. Adapted from [73].

Regarding the PLA degradation profile, It was reported that this biopolymer has a relatively shorter degradation time (2–6 months) when compared to PCL (more than 24 months) [156]. Although this thermoplastic polymer degrades in the body, the rapid degradation of PLA in vivo has been shown to produce LA concentrations that can trigger inflammatory responses, which may hinder cell proliferation and differentiation [157]. Therefore, controlling the degradation rate from weeks to years by adjusting the initial molecular mass, crystallinity, and copolymer ratios should be considered to resolve this issue [55]. Table 5 summarises the key mechanical properties of PLA, PLLA, and PDLLA. Although several methods for synthesising PLA, such as direct polycondensation, azeotropic dehydration condensation or ring opening polymerisation are known, none of them are straightforward or easy to implement [155]. Figure 3 illustrates three pathways through which PLA can be synthesised. These methods require the use of catalysts under carefully controlled conditions of temperature, pressure, and pH, along with extended polymerisation times, making it a highly energy demanding process [1].

Table 5. Key PLA physical and mechanical properties [155].

Property	PLA	PLLA	PDLLA
Melting temperature, (°C)	150–162	170–200	Amorphous
Glass transition temperature (°C)	45–60	55–65	50–60
Ultimate tensile strength, (MPa)	21–60	15.5–150	27.6–50
Tensile modulus (GPa)	0.35–0.5	2.7–4.14	1–3.45
Ultimate tensile strain (%)	2.5–6	3.0–10.0	2.0–10.0
Specific tensile modulus (kNm/g)	0.28–2.8	0.80	2.23–3.85

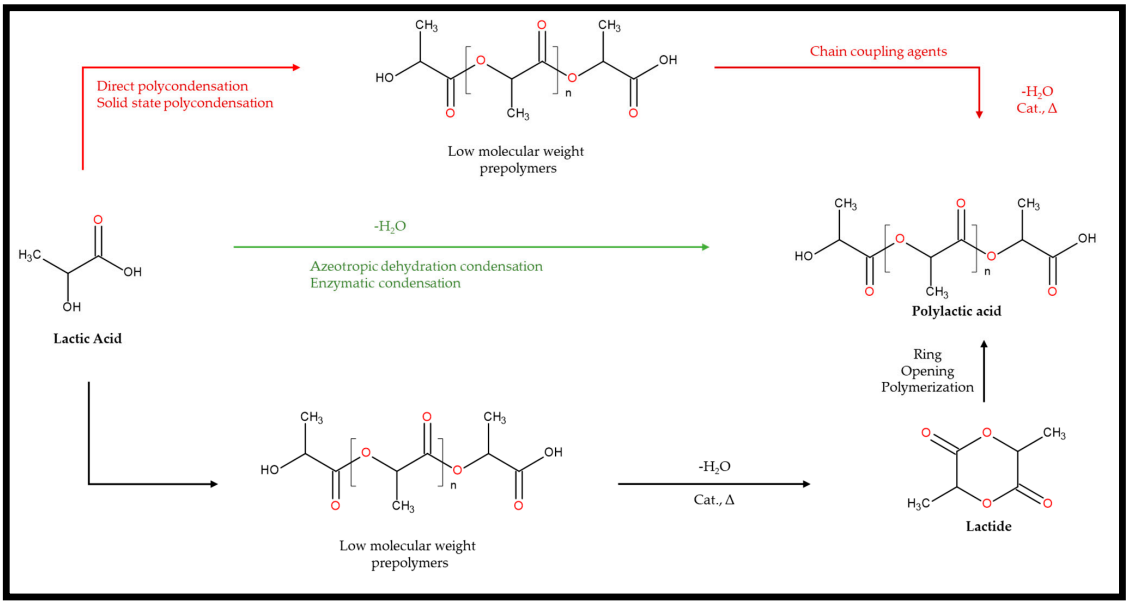


Figure 3. PLA synthesis pathways: As shown above, PLA can be synthesised from LA monomers using various pathways, including direct polycondensation, azeotropic dehydration condensation, or ring-opening polymerisation. These processes occur under controlled conditions such as temperature, pressure, and pH, with the presence of a catalyst. Adapted from [155].

Beyond its key role as a building block of PLA, lactic acid is also known to affect cellular functions in the body. Being a small and nonpolar molecule, it can easily cross the cell membrane lipid bilayer and be converted into glucose inside the cell where it acts as an energy source. Due to its outstanding properties, notably mechanical and biological properties, as well as its thermoplastic potential, PLA is the most commonly used synthetic biomaterial, with notable mounting biomedical applications once it undergoes some chemical modifications [1]. This biomaterial is widely used in the production of drug delivery systems, bioresorbable implants and sutures, as well as scaffold membranes for tissue engineering. It plays a key role in aiding the recovery of biological functions in damaged cells, tissues, and organs within the body [153].

In a study aimed at designing a prototype degradable medical device to prevent the formation and recurrence of IUAs, a biodegradable film made from the PLA-(b)-PEG-(b)-PLA copolymer was created and compared with an HA gel sample. The results showed that the three-block copolymer swelled within the uterus and was fully degraded within 12 days. Furthermore, unlike the HA hydrogel, it effectively prevented adhesion formation and promoted endometrial repair [72].

The extensive clinical use of PLA-based products is partly due to its approval by the U.S. Food and Drug Administration (FDA) for direct contact with biological fluids [153,155]. PLA has been utilised in the production of various medical devices and implants. Given this, researchers have emphasised the importance of considering factors such as PLA's degradation profile, cytotoxicity, tensile strength, and elastic modulus. For instance, while assessing the effect of blending PLA with polyacrylates in a 1:1 weight ratio, the analysis performed disclosed that the blends were highly crosslinked, rigid, and heterogeneous, with some exhibiting semicrystalline properties. Additionally, it was found that the PLA-polyacrylate blends displayed greater photostability compared to pure PLA [158].

5.8. Polyglycolic Acid

Polyglycolic acid (PGA) is a biodegradable and biocompatible polymer known for its exceptional rigidity, strength, tensile modulus, abrasion and solvent resistance as well

as excellent gas barrier capabilities [133,159,160]. In comparison with the previously discussed synthetic biomaterials, PGA has extraordinary mechanical properties. This polymer has a tensile strength of 109 MPa together with a tensile modulus of 7.0 GPa. Table 6 illustrates the main physical and mechanical properties of PGA. Notably, these properties make PGA well-suited for various fields in biomedical applications, although its high production cost limits its widespread use [161]. While this biomaterial has one of the simplest structures, its physicochemical and mechanical properties enable it to deliver exceptional performances [159]. Limited thermal stability and poor mechanical properties are among the key challenges encountered while exploiting its therapeutic potential in biomedicine [162].

Table 6. Main PGA physical and mechanical properties [160].

Property	PGA
Melting temperature, (°C)	220
Glass transition temperature (°C)	40
Heat deflection temperature (°C)	168
Tensile elongation, (%)	2.1
Tensile modulus (GPa)	7.0
Tensile strength (MPa)	109

However, efforts have been made to overcome the limitations of PGA related to limited thermostability. In this regard, PGA has been modified through copolymerisation, physical blending, or multilayer lamination, resulting in a PGA–PLA copolymer that combines the enhanced mechanical strength of PLA and the improved thermostability of PGA. Although this copolymer offers promising benefits, the process is still expensive, and, as a result, the material has not seen widespread use in biomedical applications [161]. Another study focused on copolymerising glycolic acid with a small amount of ε-caprolactone through melt polycondensation to create random poly (glycolic acid-co-ε-caprolactone) copolymers. These copolymers exhibited enhanced thermal stability, preventing significant thermal degradation during the polycondensation and processing stages. This marked the development of the first PGA-based material with a wide processing temperature range, high molecular weight, and enhanced performance through melt polycondensation [159].

PGA is known to have a significant role in tissue engineering, where it can serve as a structural framework that supports cell growth and tissue regeneration while gradually degrading to allow for the integration of new tissues. This material is commonly used in drug delivery systems, especially in the production of implantable devices, as PGA-based microspheres or nanoparticles can offer controlled and sustained drug release at the target site [134]. The use of PGA as an animal-free biomaterial scaffold for 3D endometrial cell cultures was compared with the widely used natural fibrin–agarose. After culturing primary endometrial cells on both fibrin–agarose and PGA scaffolds, the results showed that both materials could replicate the natural human endometrium, promoting the growth and proliferation of endometrial cells on each scaffold [64]. Although this should serve as a foundation for PGA applications in regenerative medicine, especially for endometrial repair or regeneration, research and development of 3D scaffold materials still encounter challenges. These include high production costs and a lack of consensus on the ideal porosity and pore size for various materials needed to effectively repair defects [64].

A comparative study was carried out to compare the capacity of fibrin–agarose and polyglycolic acid as an animal-free biomaterial for the three-dimensional culturing of human endometrial cells. The study findings revealed that endometrial cells grew and proliferated on both scaffolds after 7 days of culturing. All of these findings confirmed that

both scaffolds mimicked the human endometrium. Nonetheless, due to environmental and ethical issues, as well as the low cost of synthetic polymers, the authors recommended greater use of PGA scaffolds [64]. The clinical benefit of PGA in nerve cell regeneration was explored. It was found that PGA conduits could promote the regeneration of nerve cells, which was followed by their effective biodegradation [163]. Nonetheless, further research and innovations are needed to enhance the stability and biocompatibility of PGA, particularly due to its rapid degradation and the reported inflammatory responses triggered when PGA and PGA-based materials are used. This will be crucial for achieving optimal clinical application of these products while ensuring patient safety and health outcomes.

It is evident that the real-world application of PGA and PGA-based products is still a long way off. Therefore, research and development should prioritise discovering new, innovative, and cost-effective sources of glycolide monomers, which are the key raw materials for PGA synthesis. By doing so, the production costs of PGA and PGA-based materials could be significantly reduced, making these materials more accessible and commercially viable for a broader range of applications. This could equally involve revolutionising government policies regarding bioplastics, exploring alternative feedstocks such as industrial waste, improving synthesis processes, or developing sustainable manufacturing techniques that not only lower costs but also enhance the overall sustainability of the PGA production process [161].

5.9. Carboxymethylcellulose

Carboxymethylcellulose (CMC) is a polymer composite derived from cellulose natural polymer that is gaining increasing attention for its applications in various fields, particularly in tissue engineering and drug delivery [164,165]. CMC is an ionic and water-soluble biopolymer currently considered as the most common additive, particularly since it is less expensive and easily applied in various applications. In addition, it is synthesised from cellulose, the most abundant polymer in the world via alkalisation and etherification reactions [165,166]. Regarding the chemical structure of CMC, the repeating units in this polymer are linked by β-1,4-glycosidic linkages. The key structural difference between CMC and cellulose is the presence of anionic carboxymethyl groups in CMC, which replace the hydrogen atoms of certain hydroxyl groups found in cellulose [165]. Thus, this biopolymer contains a hydrophobic polysaccharide backbone along with many hydrophilic carboxyl groups, allowing its amphiphilic characteristic. CMC exhibits varying degrees of substitution and molecular weights, which are key factors that determine its properties and applications. Figure 4 illustrates the structure of CMC. It has been reported that an increase in the degree of substitution is directly proportional to an improvement in the compatibility of CMC with other materials [167].

CMC offers strong mechanical properties and resistance to degradation in vivo, along with reactive surfaces that enable protein binding through controlled surface chemistry. It also demonstrates biocompatibility, supporting both granulation tissue and bone formation. Nevertheless, It was reported that its mechanical strength, viscosity, and rheological properties limit the range of applications for synthesised CMC products. As a result, they recommended effective characterisation of CMC products as a crucial step in determining its potential applications [165]. Recognised as a promising biomaterial in biomedical applications, CMC is particularly valued for its ability to undergo chemical modifications, which enhance its physical, chemical, and mechanical properties to suit specific and tailored applications [164]. With an aim to enhance the applicability of CMC while addressing their issues related to poor degradation profile, this polymer was combined with other biomaterials to produce biopolymer composites or scaffolds with desired properties [164]. It has been reported that CMC is valuable in various industries, including biomedical, phar-

maceutical, food, and oil sectors. Moreover, its effectiveness in these fields is significantly influenced by factors like purity, degree of polymerisation (DP), degree of substitution (DS), and uniformity, which impact the performance of the resulting products, such as solubility, particle size, viscosity, and rheological properties.

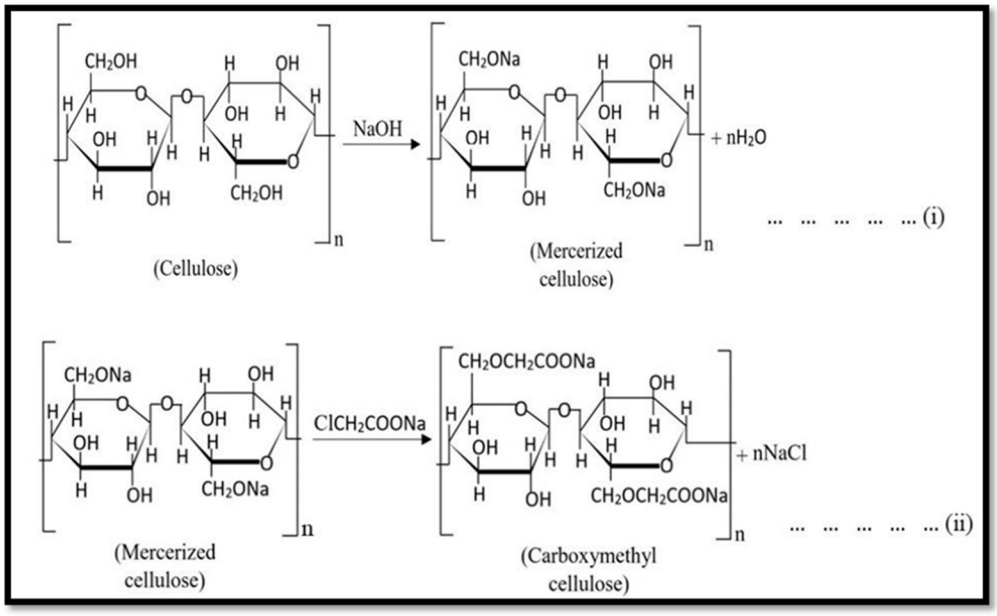


Figure 4. Illustrates a two step-synthesis route of CMC from cellulose via (i) mercerisation and (ii) etherification reactions. The figure highlights the replacement of hydrogen atoms in of hydroxyl groups of cellulose by anionic carboxymethyl groups in CMC. Adapted from [165].

For instance, composite gels and films made from CMC and polyethylene oxide (PEO) have been developed for use in separating healing tissues. These materials have been shown to reduce postsurgical adhesions in animal models of adhesion formation [168] and the high porosity and excellent biocompatibility of these scaffolds supports cell adhesion and migration, while also promoting tissue regeneration [164]. Two clinical studies evaluating the efficacy of CMC–PEO copolymers in managing IUAs have shown promising results. In the first study, 110 IUAs eligible for surgical treatment were randomly assigned to two groups. Group 1 underwent hysteroscopy followed by application of Intercoat (CMC–PEO), while group 2 received hysteroscopy alone. One month later, office hysteroscopy revealed a significant reduction in both the incidence (6% vs. 22%; $p < 0.05$) and severity (33% vs. 92%) of IUAs in group 1 compared to group 2 [169]. Similarly, women undergoing hysteroscopy for retained products of conception (RPOC) were randomly assigned to two groups. In the first group, 26 women received Intercoat, while the second group of 26 women received no treatment. The results showed that moderate-to-severe adhesions developed in one woman (4%) in the treatment group, compared to three women (14%) in the control group. After a 20-month follow-up, seven women (27%) in the treatment group became pregnant, compared to three women (14%) in the control group [170]. More clinical studies are required to validate the safety and efficacy of CMC and CMC-based products with therapeutic potentials in the field of tissue engineering and, particularly, reproductive medicine.

6. Challenges for Clinically Relevant Biomaterials and Their Derivatives

6.1. Limitations in Physicochemical and Mechanical Properties as Well as Recent Advances

Notwithstanding the increasing biomedical applications of biomaterials and their derivatives in developing treatments for various medical conditions, it is evident that the

use of these materials has been linked to some drawbacks. Thus, there is a need for further research in material science and tissue engineering to find strategic remedies for them. Table 7 summarises some naturally occurring biopolymers, sources, key characteristics, advantages and drawbacks in biomedical applications. As noted earlier, HA has been reported to have various biomedical applications. However, the limited mechanical strength of HA was found to interfere with some of its applications.

Once in non-crosslinked form, HA has a shelf-life of only 24–48 h in the body. This is due to HA being rapidly degraded by hyaluronidase enzymes [7,109], which potentially limits its residence time at the action site and bioavailability. In response to this, it has been reported that, due to its simple structure, the main chain of HA can be chemically modified primarily at the hydroxyl and carboxyl ends, which can increase its stability in vivo. Crosslinking and bioconjugation methods can nowadays allow for the precise tuning of various HA properties, such as mechanical, rheological, and swelling behaviours, while widening its biomedical applications. Additionally, these modifications help protect the polymer from enzymatic degradation and increase the biomaterial's residence time and bioavailability at the therapeutic site [3].

Similarly, Buckley et al. (2024) revealed that chemical modification of HA by thiolation and methacrylation increased HA receptor interaction while improving the mechanical strength required for peripheral nerve regeneration. Additionally, HA chemical modification leads to tailored biodegradation, increased adhesiveness, and allows crosslinking and bioconjugation [88]. Likewise, acetylated hyaluronic acid-divinyl sulfone hydrogels have been identified as an innovative approach to enhance the physical properties of HA while increasing its retention time and therapeutic effect [7]. Limited cell adhesion and an inability to undergo UV-induced photo-crosslinking hinder HA's therapeutic effects and biodegradability. To address this, modifying HA through thiolation and methacrylation was proven to enable the creation of a new photo-crosslinkable polymer, offering enhanced physicochemical properties, improved biocompatibility, and the ability to tailor its biodegradation rate [88]. Thus, chemical modification of HA cannot only serve to improve its physicochemical properties and current biomedical applications, rather, it can pave the path for bioengineers and material scientists to discover its novel therapeutic applications. Equally important is the creation of new HA formulations and delivery methods to improve their stability, bioavailability and therapeutic effectiveness in preventing and treating reproductive disorders, especially female IUAs.

ALG is known for physicochemical and mechanical weaknesses which reduce its biomedical application potential. To enhance its therapeutic efficacy and broaden its applications, ALG should be chemically modified or combined with other biomaterials to improve cellular compatibility, gelation properties, biodegradability, and mechanical strength [55]. Nevertheless, the deformability of ALG is influenced by its structural composition. It was reported that ALG with rich M-blocks is more flexible and deformable than ALG with more G-blocks [118]. This implies that material scientists should choose M-blocks-rich ALG when seeking to modify this biopolymer for targeted biomedical applications. ALG's chemical modification by crosslinking, which occurred at 23 °C, improved its biodegradability in artificial urine. Using both barium and calcium ion crosslinkers, instead of calcium ions alone, resulted in a hydrogel with enhanced tensile strength, which in turn influenced the resorption rate and swelling properties. This led to a more improved degradation profile of the biopolymer. A better degradation profile makes ALG better suited to its use, particularly in drug delivery systems [121].

Table 7. Common natural and synthetic biomaterials, biomedical applications and limitations. T_m = melting temperature.

Biomaterial	Nature	Source	T_m (°C)	Applications/Advantages	Disadvantages	Reference
Natural Materials						
HA	Polysaccharide-based	Mainly in extracellular matrices of vertebrates and humans	N/A	Reproductive and regenerative medicine Tissue engineering Drug delivery Endometrial regeneration Abundant in ECM High biocompatibility and fluidity	Rapid degradation Limited mechanical strength Immunosuppressive and antiangiogenic (long chains)	[107,109]
ALG	Polysaccharide-based	Seaweed and bacterial origin	99	FDA approved and Ph. Eur adopted Stable in the form of hydrogel Facilitate cell encapsulation and 3D printing Artificial ovaries making Drug delivery systems High level of deformability Relatively less expensive	Limited degradation and renal clearance Deficiency in the property of cell adhesion Limited ability to promote cell migration and cell adhesion Cannot be used alone	[118,119]
Chitosan	Polysaccharide-based	Crustacean shells	102.5	Wound dressings Haemostatic properties Implants Tissue engineering Drug delivery systems	Limited mechanical strength Poor water resistance, and low thermal stability	[124,171]
Collagen	Protein-based	ECM component in mammals and aquatic organisms	71–96	Cell adhesion and regeneration Amenability to modifications cells and drug delivery systems	Low mechanical stability Cannot be used alone	[138]
Gelatine	Protein-based	Extracted from bones, skin, and connective tissues of animals	40	Excellent gelation Flexible for modifications Promote cell proliferation Low cost	Low thermal stability and weak mechanical strength	[89,142]
Fibrin	Protein-based	Blood component	71	Functions in blood clotting and Wound healing Anti-inflammatory Cell regeneration Excellent stiffness High viscosity, elasticity Biocompatibility	Limited long-term stability Standardisation, reliability issues and structural stability issues	[103,144,145]

Table 7. *Cont.*

Biomaterial	Nature	Source	T_m (°C)	Applications/Advantages	Disadvantages	Reference
PLA	Polymer of lactic acid	Extracted from sugar cane, corn, cassava and maize or synthesised via direct polycondensation, azeotropic condensation or ring opening polymerisation	170–180	FDA-approved Used as Implants Good biodegradability Excellent mechanical properties and chemical stability Less expensive The most used poly-lactone	Complex synthesis Rapid degradation Can elicit inflammatory responses from acidic by-products High permeability of gases or vapours via PLA films	[1,74]
PGA	Polymer of glycolic acid	Synthesised via melt polycondensation or ring opening polymerisation	220	FDA-approved Excellent mechanical strength, solvent resistance as well as excellent gas barrier capabilities	Glycolic acid accumulation can elicit inflammation and lead to impaired cell proliferation and differentiation High production cost Reduced toughness, and rapid hydrolysis and biodegradation Thermal instability	[54,161,162]
CMC	Polysaccharide-based	Synthesised from plants via alkalisation and etherification reactions	274	Biocompatibility Common additive Less expensive Derivative of cellulose, the most abundant polymer Strong mechanical properties	Poor degradation profile Limited viscosity, and poor rheological properties	[164–166]

Chitosan has known increasing application in various medical fields including tissue engineering. However, by itself it offers limited health benefits. This is mainly due to its limited mechanical strength [171]. However, combining it with other biopolymers, such as ALG, HA, collagen, PEG, chitosan to name a few, can enhance its characteristics, expanding its therapeutic applications. For example, blending chitosan with ALG creates a polyelectrolyte complex scaffold with markedly improved modulus, strength, and stability. Equally noteworthy, a fused filament fabrication-based 3D printing technology was employed to combine chitosan and PLA, aiming to overcome the limitations of chitosan's weak mechanical properties and PLA's natural hydrophobicity and lack of essential functional groups for biological activity. The resulting PLA–chitosan composites were shown to be both mechanically and biologically effective, making them more promising for clinical applications [171].

Collagen possesses excellent properties that make it reliable for various biomedical applications, though it is not advised to use it on its own. This is because collagen has limited mechanical stability and requires extended crosslinking time due to its slow gelation process [116]. Also, type I collagen self-assembles into fibrous hydrogels at 37 °C, making its processing tedious. However, blending collagen with other biopolymers has resulted in blends with improved properties. Collagen-based polymeric composites have shown significant potential in tissue engineering, especially for regenerating skin and cartilage [116]. For example, the application of collagen and HA polymeric composites were reported to result in improved cell proliferation, migration and cell functions. Additionally, in a mouse model, in an effort to address the issue of skin grafting with limited duration at the graft site, a mixture of epidermal keratocytes and dermal fibroblasts mixed with collagen showed promising results in wound healing and regenerating the skin [172,173].

Gelatine's biomedical application in drug delivery, scaffolds for tissue regeneration, and wound dressings has been reported in the literature [134]. However, the challenges related to its low thermal stability and weak mechanical strength remain the hindering factors to the biomedical application of this biopolymer [103]. This is because these drawbacks often necessitate modifications and blending with other materials which require advanced processing techniques while increasing the production cost. Apart from this, chemical modification of gelatine by blending it with other biopolymers has been identified as a promising approach to improve its mechanical properties and biomedical application.

PLA is among the most common polymers specifically used in the medical device industry. However, this biopolymer has slow degradation (2–6 months), specifically when compared with its counterpart, PCL (more than 24 months) [156]. PLA's slow degradation rate, hydrophobic nature, high permeability to gases and vapours through its films, and low impact toughness are recognised as major limitations of this biomaterial [155,158], which dictate continuous research for the improvement of PLA properties. However, it was reported that chemical modifications of PLA, through either copolymerisation, grafting, crosslinking, UV-irradiation, plasma treatment, or physical methods, like heating and blending with various modifiers, potentially alleviate PLA weaknesses [158].

Fibrin is considered one of the groundbreaking biomaterials with significant biomedical applications. Its use in biomedical fields is expected to continue expanding, as existing research indicates that its full biological potential has yet to be explored. Despite its clinical promise, fibrin faces challenges such as rapid degradation, weak mechanical properties, limited long-term stability, and issues with standardisation and reliability, which altogether hinder its wider clinical application. Researchers have suggested various ways to improve fibrin's therapeutic effectiveness, but the most common is chemical modifications its structure and composition via methacryloyl reaction, sulfonation, or sialylation or chemical crosslinking to produce fibrin with biomedically sound properties [103,174]. One of the re-

cent strategies to enhance the properties of fibrin involves blending it with other polymers. For instance, the integration of materials like pegylated fibrin and PVA-fibrin hydrogels has shown encouraging outcomes. Likewise, combining fibrin with natural biopolymers such as collagen [175], alginate, HA, laminin, elastin, and agarose has been reported to improve specific characteristics, better replicate the native ECM of target tissues, influence cell behaviour, and support tissue repair and wound healing. We refer the reader to the two recently published review articles for more detailed information on current challenges and innovations in fibrin biomedical applications particularly for wound healing and tissue engineering [84,103].

Despite its increasingly promising biomedical applications, PGA encounters common limitations such as low thermal stability, reduced toughness, and rapid hydrolysis and biodegradation, which have hypothetically restricted its wider use [161,162]. For example, limited thermal stability complicates PGA synthesis, and unlike the widely applied polylactides, even though the first PGA synthesis via melt polycondensation was performed in 1938, this biomaterial wasn't commercially produced by Kureha chemical through ring-opening polymerisation of glycolide until 2008 [160]. The synthesis of PGA through ring-opening polymerisation uses a tin octoate catalyst, and since tin octoate-catalysed reaction is rapid, it helps prevent potential thermal decomposition of PGA [162]. Nevertheless, a key challenge for PGA manufacturers remains the efficient and lucrative production of the glycolide starting monomers. As a result, global production of PGA is still limited, and its applications are confined to very few areas, including biomedical applications [159]. To overcome the challenge of PGA thermal instability, the polymer is modified through copolymerisation, physical blending, or multilayer lamination, resulting in a PGA–PLA copolymer that combines the enhanced mechanical strength of PLA and the improved thermostability of PGA even though this process is not cost-effective [161].

Similarly, the therapeutic role of CMC has been emphasised in the literature. CMC offers strong mechanical properties and resistance to degradation in vivo, along with reactive surfaces that enable protein binding through controlled surface chemistry. It also demonstrates biocompatibility, supporting both granulation tissue and bone formation [163]. Nevertheless, Rahman et al. (2021) reported that its mechanical strength, viscosity, and rheological properties limit the range of applications for synthesised CMC products. As a result, they recommended effective characterisation of CMC products is a crucial step in determining its potential applications [165].

6.2. Regulatory and Clinical Translational Challenges for Biomaterial-Based Products

Biomaterial-based devices are implanted each year, helping to save millions of lives around the world. Although the demand for biomaterials and their use in treating various medical conditions continues to grow, several challenges still limit their widespread clinical applications. These challenges are related to manufacturing difficulties, complex and inconsistent regulatory processes across countries, surgical implantation failures, biocompatibility once into contact with the physiological environment and high costs [52]. This highlights the need for ongoing research to address these challenges and enhance the translational application of these lifesaving products. One of the most notable characteristics of biomaterials is their ability to coexist with body tissues without causing severe adverse effects for diagnostic or treatment purposes [53]. The outstanding biological properties of these biomaterials, such as high biocompatibility, biodegradability, low toxicity, and minimal immune response, make them clinically valuable. Nonetheless, their close interaction with the body's physiological environment means that any failure can lead to serious consequences. According to the literature, ensuring biocompatibility has remained a significant challenge for both manufacturers and users of these biomaterial products [2,8,173].

The ISO 10993-1 part of the series outlines the criteria for selecting appropriate in vitro and in vivo methods for preclinical testing of a device's biological safety. The remaining 22 parts of the series offer detailed recommendations on various chemical, physical, and biological methods to ensure thorough biocompatibility assessment [176]. This biocompatibility mainly depends on factors such as the duration of biomaterial contact with biological systems, its chemical composition, mechanical properties, and physical form. Although the medical device industry is highly regulated, evaluating the biocompatibility of biomaterial-based devices remains a complex task. This difficulty is largely due to factors such as the material's chemical composition, physical characteristics, the type of tissue it contacts, and the length of that contact. Nevertheless, in addition to ISO 10993-1, the adoption of ISO 15499:2012 "Biological evaluation of medical devices—Guidance on the conduct of biological evaluation within a risk management process" [177] to ensure the careful selection of in vitro tests during the development and manufacturing stages has been suggested as a viable and sustainable strategy [177,178].

Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR) in the European Union (EU) are the regulatory bodies responsible for the regulation of biomaterial-based medical devices [179,180]. The regulatory approval for biomaterial-based products, including biomedical devices and implantable drug delivery systems, remains a significant challenge, particularly in Europe, where early regulatory involvement slows the process and increases costs, delaying market entry; this has resulted in a large number of companies neglecting the European market for their biomedical devices' introduction. According to a 2022 MedTech Europe survey, around 23% of medical device recalls in 2023 occurred in the EU. Therefore, this highlights the critical need for stringent regulations and strong post-market surveillance to ensure patient safety and public health protection from substandard, poor quality and unsafe products [181]. Apart from the ISO 10993, biomedical devices are regulated under Regulation (EU) 2017/45 of the European Parliament and the Council of 5 April 2017 on medical devices [182]. All these ensure that robust assessment is carried out before a biomaterial-based product enters the European market.

In the United States (US), the Food and Drug Administration (FDA) conducts pre-market assessments to determine whether there are potential adverse biological reactions and whether the associated risks are unacceptable when a biomaterial-based medical devices come into contact with the body. Also, the FDA ensures strengthened post-market supervision of potentially high-risk products through post-market follow-up and evaluation of marketed medical devices [183,184]. While the ISO 1099 standard is valid for biomedical devices on the U.S. market, this is complemented by FDA recommendations on the use of ISO 10993-1, "Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process", which was issued on 16 June 2016 [182,183].

Despite the established regulatory pathways and progress in the design and development of biomaterials and related products, including conducting biomaterial structure-function and preclinical studies, the link between the obtained findings and the actual therapeutic effectiveness or regenerative outcomes in humans remains largely unexplored and uncertain. Therefore, insights from identified mechanisms of action, in addition to establishing scientifically sound design parameters, and incorporating existing translational insights into biomaterials development, will help optimise the creation of innovative materials which meet regulatory requirements and address upcoming medical challenges [185].

Equally important, several other guidelines for the evaluation of materials are known to contribute to ensuring the quality of biomaterials used in the development of medical devices and implants. These include the American Society for Testing of Materials (ASTM), Association for the Advancement of Medical Instrumentation, U.S. or European Pharmacopoeia, and National Institute of Standards and Technology [53]. Nevertheless,

irrespective of the relevance of these organisations to ensuring the safety and effectiveness of the developed products, the greater the variability in requirements across different organisations and countries, the more complex the process of translating biomaterials becomes. Also, despite significant efforts to enhance the production of various biomaterial-based products for clinical use, only a small number successfully navigate the complex regulatory landscape to reach the market. Also, long-term monitoring is essential to detect potential delayed adverse effects, which can influence marketing strategies. Unfortunately, several products have been recalled after years of clinical use. This highlights the urgent need to streamline regulatory processes and standardise biomaterials to ensure safety and efficiency [53].

A 2012 survey in the U.S. on the obstacles to commercialising tissue engineering products revealed that the main challenges include limited financial resources, especially for smaller companies, complex regulatory processes, difficulties in clinical translation, and issues with obtaining reimbursement from medical insurance companies for these innovative products [185]. The biomaterial-based reimbursement issue is also encountered in Europe. A review on the Belgian consensus on adhesion prevention during hysteroscopy and laparoscopy noted that although Hyalobarrier Gel Endo®, by Anika therapeutics, INC. in Padova (Italy), and Intercoat® Nordic Pharma, Paris, (France) biomaterial-based devices have demonstrated significant effectiveness in reducing adhesions, they are not eligible for reimbursement. Consequently, it was suggested to use optimal surgical techniques, administering oestrogen for 10 days after adhesiolysis, and considering the potential role of non-steroidal anti-inflammatory drugs and/or corticosteroids commonly used for pain management in preventing postoperative adhesions too [114].

Furthermore, the translational application of biomaterials and their derivatives have faced ethical issues. Most novel biomaterial-based products, including biomedical devices, are not cost-effective and, thus, are inaccessible patients. Also, the use of animal studies during the development of biomedical devices and implants was reported to be ineffective, not only because of the traumas caused to animals but also the fact that the complex immune, mechanical and cellular factors in animal models cannot always be mimicked when assessing host-biomaterial interaction in vitro. However, current advances in organ-on-a-chip technology, microfluidics, and bioprinting are the promising solutions to these issues [186]. Another challenge for biomaterials in biomedical use is that their full therapeutic potential often becomes clear only after clinical application, when key effectiveness parameters can be identified for future improvements [76,179].

Therefore, understanding early cell–scaffold interactions and the resulting biochemical signals is crucial to ensure the scaffold's quality, safety, and efficacy, as well as to support regulatory approval and market readiness. Additionally, strong post-market surveillance is essential to monitor product performance, quickly identify failures, and initiate recalls before serious harm occurs to patients [76]. The recent progress in biopolymer technologies, including 3D printing and advanced biomaterials like bioresorbable and smart materials, has significantly improved medical treatments. However, some regulatory challenges continue to limit their routine clinical use. Although some 3D-printed medical devices have been approved globally, no 3D-printed tissues or organs have received regulatory clearance. This is largely due to issues such as lack of standardisation, limited expertise, logistical barriers, and uncertain long-term safety. As healthcare moves toward personalised solutions, careful consideration of processes, materials, and regulatory compliance is essential for developing patient-specific 3D-printed implants and tissues [83].

Moreover, other factors, such as limited research facilities, medico-legal concerns, data confidentiality issues, conflicts of interest, plagiarism, shortage of human resources, cultural or religious influences, as well as emerging technologies have been reported to hinder

the clinical application of biomaterial-based medical devices, particularly in the fields of tissue engineering and regenerative medicine [53]. Thus, considering the points discussed, stringent regulatory oversight of biomaterials and their derivatives is essential to safeguard patient health, especially since their medical application is still emerging. Nonetheless, advancing their integration into clinical practice requires multinational cooperation and partnership and close collaboration among manufacturers, regulatory authorities, insurers, as well as patients.

7. Marketed Biomaterial Products for Cell/Tissue Regeneration

Several biomaterial-based products have been developed and approved for use in preventing or treating various medical conditions and complications resulting from surgical procedures [53,54,116,187]. These products are commonly used as anti-adhesives to prevent the formation of fibrous tissues due to an abnormal wound healing process, while contributing to effective tissue regeneration [73]. Traditional physical barriers were found to be insufficient in alleviating symptoms associated with adhesions, as well as in controlling inflammation and promoting cell regeneration. To address these challenges, biomaterial-based products were developed to be used in combination with surgical procedures. The current biomaterial-based products include drugs such as anti-inflammatory, anticoagulant, and fibrinolytic agents, along with antibacterial agents or growth factors meant to support tissue regeneration. However, further research is recommended to evaluate the efficacy and safety of these emerging products in both animal and human subjects [73].

The effectiveness of the administered drug partly depends on its dosage form. Most of the currently available biomaterial-based products used as physical barriers to prevent adhesions in various tissues come in the form of hydrogels, biofilms, electrospun fibrous membranes, and microspheres. While each dosage form offers certain advantages, they also present some challenges such as difficult administration [15,44], rapid degradation (in the case of electrospun fibrous membranes, hydrogels and biofilms) [7], toxicity (for hydrogels crosslinked with chemical agents), and instability of incorporated proteins and peptides (in microspheres) [73]. Therefore, exploring novel dosage forms, administration methods, and crosslinking strategies for clinically relevant biomaterials could help overcome these issues and improve their clinical effectiveness while widening their biomedical applications. For example, this could be through the development of solid dispersion implants that can ensure sustained release of the biopolymer to ensure its longer residence and higher bioavailability at the action site. Table 8 below summarises the key factors affecting release kinetics from biopolymer-based DDSs. While developing an implantable device especially from biopolymer composites, it is important to know that the stability of the drug, its bioavailability and therapeutic effect at the action site are all influenced by the properties of the drug itself, the biopolymer matrix (carrier) as well as the surrounding environment [188].

Biomaterial-based products available on the market include those designed to manage adhesions in various parts of the body, including pericardial, tendon, abdominal, and pelvic regions. These biomaterial-based barriers do not directly interfere with the biological process of adhesion formation. Instead, they function primarily as physical spacers, keeping wound surfaces apart during the early stages of healing, thereby lowering the likelihood of adhesions developing [19]. For instance, Womed leaf composed of PLA and PEO is an IUA barrier film developed by the Institut des Biomolecules Max Mousseron in France, to prevent the formation of IUAs post intrauterine procedures. A preclinical study conducted on rats to assess the safety and efficacy of Womed Leaf showed that the implant did not enhance endometrial thickness or reproductive outcomes when comparing the treatment

group to the control group. However, it was confirmed that Womed Leaf did not induce irritations and efficiently showed potential to prevent IUAs formation [81].

Table 8. Summarises the key factors affecting release kinetics from implantable drug delivery devices [188,189].

Parameters	Effects
1. Drug properties	
Hydrophilicity/hydrophobicity Diffusion/dissolution characteristics Charge Stability Solubility in biopolymer matrix	Impacts the aqueous solubility, which subsequently influences various factors such as protein binding, tissue retention, localised drug concentration, and the kinetics of drug release.
2. Biopolymer properties	
Thermal property Degree of crystallinity Molecular weight	Biopolymers influence degradation, hydrophobicity, drug release, and drug solubility.
3. Release medium	
pH Temperature Ionic strength Enzymes	Influences the degradation profile of biopolymers and the solubility of drugs.

Moreover, this minimally invasive device is inserted into the uterus through the cervix and is naturally expelled after use. In a clinical study aimed at evaluating the efficacy and safety of Womed Leaf, the device successfully prevented the formation of IUAs, and no cases of uterine perforation or cervical trauma were reported, confirming the implant's efficacy and safety. However, the clinical data suggest that the tested device, measuring 4.5 cm in length, is insufficient to cover the entire uterine cavity due to significant variations in the sizes and shapes of women's uteruses [82]. However, a recent RCT published in 2024 assessed the effectiveness of Womed Leaf in women with moderate-to-severe IUAs undergoing hysteroscopic adhesiolysis. This study, which included 160 participants (75 in the treatment group and 85 in the control group), found that the absence of IUAs was significantly higher in the treatment group (40%) compared to the control group (21%). Additionally, the use of the biodegradable polymeric film was not linked to any serious adverse events, and even the mild events observed were not considered related to the device [190].

Seprafilm® developed by Baxter International Inc, Pennsylvania (in USA), a solid physical barrier composed of both HA and CMC, has been approved by the FDA and CE for use in pericardial, peritoneal, and tendon adhesions. Additionally, Interceed®, developed by Ethicon, Somerville, NJ, (USA), a solid barrier made from oxidised cellulose, Adept®, developed by Baxter, Dearfield, IL, USA, a liquid barrier containing high molecular 4% Icodextrin, and SurgiWrap®, developed by MAST Biosurgery, a PLA-based solid gel, have all been FDA and CE-approved and are currently used for preventing postsurgical adhesion formation [19,73,191]. A systematic review was performed to assess the long-term safety and effectiveness of adhesion prevention agents in pelvic and abdominal surgeries by analysing clinical trials and meta-analyses. The review found that with Icodextrin and Seprafilm® the bioresorbable membranes significantly decrease the occurrence and severity of adhesions, especially in high-risk surgeries. However, while there is potential for these biomaterials to help reduce postoperative morbidity and improve recovery, the need for further research was recommended to evaluate their long-term therapeutic effects, particularly concerning reproductive outcomes and chronic pain [192].

Further, Hyalobarrier®, developed by Anika therapeutics, INC. in Padova (Italy), a crosslinked HA gel approved by CE, is known as a gel barrier used in the management of IUAs.

A study comparing the efficacy of 4DryField and Hyalobarrier® for preventing the recurrence of IUA following hysteroscopic adhesiolysis in patients with Asherman's syndrome found that both biomaterials were effective in preventing the recurrence of adhesions and enhancing reproductive outcomes, particularly in terms of restoring menstruation [73,193]. However, based on the available clinical evidence, it has been recommended that additional research is needed to optimise adhesion management. This could involve advancing the development of multifunctional biomaterials by incorporating multiple drugs into the biopolymer complex to address various adhesion-related issues. Additionally, selecting the appropriate biomaterials and conducting safety studies on their by-products could enhance adhesion management [155]. Ultimately, any developed health technology should prioritise ensuring the treatment is affordable and free from adverse effects for patients.

In an RCT, the efficacy and effectiveness of the intrauterine application of Intercoat (Oxiplex/AP gel) was evaluated among women who underwent hysteroscopic treatment due to the RPOC. Following 6–8 weeks of the treatment, it was observed that the gel application did not lead to any complication postoperatively. Among the twenty-six women in both the control and treatment groups, moderate-to-severe adhesions developed in one woman (4%) in the treatment group and three women (14%) in the control group ($p = 0.80$). Similarly, over a 20-month follow-up period, seven women (27%) in the treatment group conceived, compared to three women (14%) in the control group ($p = 0.50$). Although the sample size was small and the statistical difference in adhesion prevention between the two groups was limited, the results support the safety of Intercoat and its potential effectiveness in reducing adhesions and enhancing reproductive outcomes after hysteroscopic treatment for women with RPOC [170]. Table 9 summarises some marketed biopolymer-based products' clinical application in postsurgical adhesions management, emphasising their trade names, manufacturers, clinical efficacy and safety as well their regulatory status.

Biomaterial-based products available on the market include those designed to manage adhesions in various parts of the body, including pericardial, tendonous, abdominal, and pelvic regions. These biomaterial-based barriers do not directly interfere with the biological process of adhesion formation. Instead, they function primarily as physical spacers, keeping wound surfaces apart during the early stages of healing, thereby lowering the likelihood of adhesions developing [19]. For instance, Womed leaf composed of PLA and PEO is an IUA barrier film developed by the Institut des Biomolecules Max Mousseron in France, to prevent the formation of IUAs post intrauterine procedures. A preclinical study conducted on rats to assess the safety and efficacy of Womed Leaf showed that the implant did not enhance endometrial thickness or reproductive outcomes when comparing the treatment group to the control group. However, it was confirmed that Womed Leaf did not induce irritations and efficiently showed potential to prevent IUAs formation [81].

Moreover, this minimally invasive device is inserted into the uterus through the cervix and is naturally expelled after use. In a clinical study aimed at evaluating the efficacy and safety of Womed Leaf, the device successfully prevented the formation of IUAs, and no cases of uterine perforation or cervical trauma were reported, confirming the implant's efficacy and safety. However, the clinical data suggests that the tested device, measuring 4.5 cm in length, is insufficient to cover the entire uterine cavity due to significant variations in the sizes and shapes of women's uteruses [82]. However, a recent RCT published in 2024 assessed the effectiveness of Womed Leaf in women with moderate-to-severe IUAs undergoing hysteroscopic adhesiolysis. This study, which included 160 participants (75 in the treatment group and 85 in the control group), found that the absence of IUAs was significantly higher in the treatment group (40%) compared to the control group (21%). Additionally, the use of the biodegradable polymeric film was not linked to any serious adverse events, and even the mild events observed were not considered related to the device [190].

Table 9. Some biopolymer-based products currently approved for managing postsurgical adhesions.

Trade Name	Composition	Manufacturer	Type of Study	Efficacy/Safety	Approved Status	Ref
Seprafilm® bioresorbable membrane	Sodium Hyaluronate and CMC	Developed by Genzyme Corporation but now owned by Baxter International Inc, Pennsylvania in USA.	Meta-analysis of 13 RCTs involving 3665 subjects and comparing outcomes of abdominal surgery with and without Seprafilm.	Seprafilm significantly reduced the risk of small bowel obstruction and severity of adhesions after abdominal surgery. However, it increased the risk of anastomotic leak.	Approved for abdominal and pelvic laparotomy but not yet for intrauterine cavity (FDA & CE).	[194]
Womed Leaf drug eluting film	PLA and PEO	Institut des Biomolecules Max Mousseron in Montpellier, France	RCT comparing Womed Leaf to no treatment among 160 women scheduled for hysteroscopic adhesiolysis because of symptomatic severe or moderate adhesions.	Among 75 women in treatment and 85 in control group, it was found that the absence of IUAs was higher in the treatment group (40%) compared to the control group (21%). Also, no adverse event was found related to the device.	IUAs (CE)	[190]
Interceed®	Oxidised cellulose	Ethicon, Somerville, NJ, USA	An RCT evaluating the efficacy of Interceed as a barrier to the development of postsurgical ovarian adhesions after 55 women undergoing surgery involving the ovaries.	In total, 26 of 55 Interceed-treated ovaries were free of adhesions, compared with 14 of 55 untreated control ovaries, a statistically significant difference ($p = 0.028$).	Peritonium (CE & FDA)	[195]
Intercoat® (Oxiplex/AP Gel)	CMC and PEO	Nordic Pharma, Paris, France	A randomised control pilot study comparing women who received Oxiplex (treatment group) after hysteroscopic treatment due to RPOC versus those who received no treatment (control group).	At 6–8 weeks, no postsurgical complications were detected and post-hysteroscopy, moderate-to-severe adhesions were observed in 1 out of 26 women in the treatment group, compared to 3 out of 26 in the control group. Over a follow-up period averaging 20 months (from 2 to 33 months), seven women in the treatment group achieved pregnancy, versus only three women in the control group.	Intrauterine cavity (CE & FDA)	[170]

Table 9. *Cont.*

Trade Name	Composition	Manufacturer	Type of Study	Efficacy/Safety	Approved Status	Ref
Adept®	High molecular weight dextran and 4% Icodextrin	Baxter, Dearfield, IL, USA	RCT was performed to evaluate the efficacy and safety of Adept (4% Icodextrin solution) in reducing adhesions after laparoscopic gynecologically surgery involving adhesiolysis among 402 patients (203 in Adept and 199 in Ringer Lactate Solution, RLS group).	Adept group showed significant clinical success compared to RLS group. In infertility patients, Adept demonstrated particular clinical success compared with RL (55% vs. 33%). This was reflected in the number of patients with a reduced adhesion score (53% vs. 30%) and in fewer patients with moderate/severe adhesions (43%vs. 14%). Safety was also found to be comparable in both groups.	Gynaecological surgery, peritoneum (FDA & CE)	[191]
4DryField vs. Hyalobarrier®	Microparticles derived from purified potato starch	PlantTec Medical GmbH, Germany (Lüneburg)	RCT	Laparoscopic observation showed, that 4DryField was effective in promoting haemostasis (at first-look laparoscopy) in addition to preventing adhesion in 18 of 20 women, with only 2 revealing major adhesions (second-look laparoscopy).	Abdominal surgical procedures (FDA & CE)	[193]
4DryField	Microparticles derived from purified potato starch	PlantTec Medical GmbH, Germany (Lüneburg)	RCT was performed to evaluate improvements in fertility and pain after endometriosis resection and adhesion prevention with 4DryField® among 50 women undergoing laparoscopic resection. Subjects were randomised into treatment (with 4DryField) and control group (with normal saline).	At the second-look surgery, after deep infiltrating endometriosis resection using the gel barrier 4DryField®, 85% adhesion reduction was observed. Pain was improved after 12 months. In the treatment group, 11 patients declared and retained their wish to conceive, and 7 of these became pregnant, which corresponds to a ratio of 64%.	Abdominal surgical procedures (FDA & CE)	[196]
SprayGel®	PEG	Confluent Surgical Inc., located in Waltham, MA, USA	RCT to assess the efficacy of SprayGel, a sprayable adhesion barrier for laparoscopic and open pelvic and abdominal surgeries.	In an RCT, the gel was able to prevent IUAs among 5 out of 18 in the treatment group compared to 1 out of 13 in the control group. More studies are recommended for getting this gel approved for IUAs prevention.	Not yet approved	[197]

Seprafilm®, a solid physical barrier composed of both HA and CMC, has been approved by the FDA and CE for use in pericardial, peritoneal, and tendon adhesions. Additionally, Interceed®, a solid barrier made from oxidised cellulose, Adept®, a liquid barrier containing high molecular 4% Icodextrin, and SurgiWrap®, a PLA-based solid gel, have all been FDA and CE-approved and are currently used for preventing postsurgical adhesion formation [13,68,188]. A systematic review was performed to assess the long-term safety and effectiveness of adhesion prevention agents in pelvic and abdominal surgeries by analysing clinical trials and meta-analyses. The review found that Icodextrin and Seprafilm®, the bioresorbable membranes significantly decrease the occurrence and severity of adhesions, especially in high-risk surgeries. However, while there is potential for these biomaterials to help reduce postoperative morbidity and improve recovery, the need for further research was recommended to evaluate their long-term therapeutic effects, particularly concerning reproductive outcomes and chronic pain [192].

Further, Hyalobarrier®, developed by Anika therapeutics, INC. in Italy, a crosslinked HA gel approved by CE, is known as a gel barrier used in the management of IUAs. A study comparing the efficacy of 4DryField and Hyalobarrier® for preventing the recurrence of IUA following hysteroscopic adhesiolysis in patients with Asherman's syndrome found that both biomaterials were effective in preventing the recurrence of adhesions and enhancing reproductive outcomes, particularly in terms of restoring menstruation [68,190]. However, based on the available clinical evidence, it has been recommended that additional research is needed to optimise adhesion management. This could involve advancing the development of multifunctional biomaterials by incorporating multiple drugs into the biopolymer complex to address various adhesion-related issues. Additionally, selecting the appropriate biomaterials and conducting safety studies on their by-products could enhance adhesion management [155]. Ultimately, any developed health technology should prioritise ensuring the treatment is affordable and free from adverse effects for patients.

In an RCT, the efficacy and effectiveness of the intrauterine application of Intercoat (Oxiplex/AP gel) was evaluated among women who underwent hysteroscopic treatment due to the RPOC. Following 6–8 weeks of the treatment, it was observed that the gel application did not lead to any complication postoperatively. Among the twenty-six women in both the control and treatment groups, moderate-to-severe adhesions developed in one woman (4%) in the treatment group and three women (14%) in the control group ($p = 0.80$). Similarly, over a 20-month follow-up period, seven women (27%) in the treatment group conceived, compared to three women (14%) in the control group ($p = 0.50$). Although the sample size was small and the statistical difference in adhesion prevention between the two groups was limited, the results support the safety of Intercoat and its potential effectiveness in reducing adhesions and enhancing reproductive outcomes after hysteroscopic treatment for women with RPOC [170]. Table 9 summarises some marketed biopolymer-based products clinical application in postsurgical adhesions management, emphasising their trade names, manufacturers, clinical efficacy and safety as well their regulatory status.

Another anti-adhesive biomaterial product is SprayGel, composed of 90% water and end-modified polyethylene glycol (PEG). It has also been shown to help prevent postoperative adhesions. An RCT was carried out to evaluate the effectiveness of this sprayable barrier in both laparoscopic and open pelvic or abdominal myomectomy. Ten weeks after the intervention, the results showed that 27.8 percent of patients in the treatment group (5 out of 18) were free from adhesions, compared to 7.7 percent in the control group (1 out of 13) [197]. However, Spray gel is still under clinical study to get regulatory approval for adhesions prevention. Also, a meta-analysis of 11 clinical studies on barrier agents for preventing adhesions after gynaecological surgery found that the Interceed® barrier is safe and significantly reduces the occurrence of new adhesions and the reformation of

adhesions compared to no treatment in laparoscopy [198]. In the same study, a clinical trial demonstrated that Seprafilm® resulted in better prevention of adhesion and adhesion recurrence in the treatment group compared to the control group [199]. Although clinical evidence supporting biomaterial-based products continues to grow, there is still a noticeable gap or, at most, limited availability of long-term safety and efficacy data required for their effective integration into clinical practice. To fully harness the benefits of both current and newly developed biomaterials, particularly in reproductive medicine and the treatment of IUAs, further research in human subjects is essential. Such studies aim to generate robust long-term data to strengthen their translational relevance and ensure safe, effective use in real-world medical settings.

8. Conclusions and Future Outlook

8.1. Conclusions

IUAs significantly affect women's health by reducing fertility and causing both physical and psychological distress. These medical conditions continue to be a rising global concern and represent an unmet need in reproductive medicine, currently with no effective treatment. Hysteroscopic adhesiolysis, the standard treatment for IUAs, has been associated with growing recurrence rates and poor reproductive outcomes. To improve IUAs management, innovative approaches, like combining hysteroscopy with various physical barriers, hormone therapy, and cell therapy, have been studied. The mechanisms of action of these lifesaving products rely primarily on their ability to act as physical barriers that prevent contact between damaged uterine walls and/or function as anti-inflammatory, angiogenic, anti-fibrotic, or regenerative agents. Additionally, biomaterials can facilitate the production of various implantation biomarkers, collectively leading to enhanced reproductive outcomes in IUAs-affected women. Nevertheless, these methods have shown a number of limitations, including high costs and limited therapeutic effects which lead to adhesions recurrence, and insufficient restoration of endometrium and menstrual cycles, which potentially results in circumscribed reproductive outcomes.

The current prognosis and reproductive outcomes of IUAs are influenced by both the chosen treatment strategy and the severity of the condition. While mild-to-moderate cases tend to have more favourable outcomes, according to the literature, severe IUAs are often linked to poorer prognoses. Also, due to the absence of a definitive cure and limited public disease awareness, it is crucial to invest in educating patients about IUAs, ensure optimised use of proper surgical techniques and good surgical procedure by physicians, in addition to applying effective pre- and postoperative adjuvants to help preserve female uterine function until a more effective treatment becomes available.

Among the wide range of biopolymers, the most frequently used in biomedical applications, particularly in the medical device industry, include HA, ALG, chitosan, and gelatine [54], as well as PLA, and PGA [1]. While increasing research supports the potential of HA in treating IUAs, further improvements are needed to its physical, chemical, and mechanical properties to boost its therapeutic effectiveness and meet the rising medical demands, notably in tissue engineering and reproductive medicine. Similarly, despite their remarkable properties that make them suitable for various biomedical applications, each of the existing biopolymers has inherent downsides often related to their inherent characteristics, including poor mechanical properties, limited stability, rapid degradation, limited residence time and bioavailability at the target site, therefore reducing their therapeutic effects.

Recently, the combination of hysteroscopy and biopolymers, such as crosslinked HA hydrogels adjuvants, have demonstrated significant potential in effectively managing reproductive system disorders, particularly IUAs. This is primarily due to crosslinked HA's

physicochemical properties, excellent biocompatibility, biodegradability, cell adhesiveness and its ability to promote cell migration, proliferation, and regeneration [13]. However, issues such as limited stability and rapid degradation by hyaluronidases have resulted in a reduced residence time and therapeutic effect in preventing and treating IUAs after hysteroscopic adhesiolysis [7]. Considering these factors, further chemical modifications, blending HA with a suitable biopolymer matrix to create a well-defined biopolymer composite, and the selection of appropriate dosage form of this composite can improve HA's physicochemical, mechanical, and biological properties essential for treating IUAs, while also expanding its potential biomedical applications.

Furthermore, apart from their invaluable role in managing different devastating health conditions, several regulatory and translational obstacles have been reported in relation to the biomedical application of biopolymers and their derivatives. Common challenges in bringing biomaterials to routine clinical application include manufacturing complexities, inconsistent regulatory frameworks across different countries, reimbursement, surgical implantation failures, biocompatibility concerns when exposed to the physiological environment, evidence for long-term outcomes, and high costs that limit patient accessibility. To address these issues and enhance the effective use of clinically valuable biomaterials, we strongly advocate for cross-sector collaboration, biomaterial-based product regulatory harmonisation, revising medicine reimbursement policies to include these medical products and increasing research and training investment in this emerging field. Adopting these solutions will enhance the availability, accessibility, and affordability of biomaterial-based products, particularly for women suffering from IUAs. This, in turn, will strengthen their clinical use in healthcare settings, and improve patient outcomes and quality of life, while contributing to sustainable development goals.

8.2. Future Outlook

Tissue engineering is a rapidly growing field within regenerative medicine. This innovative medical technology has become a promising alternative for treating damaged or lost organs. It utilises the patient's own cells, cultured on a polymer scaffold, to support the regeneration of tissue from natural cells [1]. Significant advancements in material science and bioengineering have resulted in the discovery of innovative biomaterials with improved physicochemical, mechanical, and biological properties for biomedical applications. However, the pace of development of these advanced materials and health technologies has not been matched by either their clinical adoption, nor by the increasing complexity of medical conditions [122]. Additionally, there are still reported limitations of clinically relevant biomaterials, highlighting the need for ongoing research in this field.

Recent reports suggest that, due to insufficient biomaterial research, particularly in reproductive medicine, and the complex requirements and dynamic function of the uterus, a suitable biopolymer scaffold or effective anti-adhesive for treating IUAs has yet to be developed [73]. Increased efforts have been made to manage IUAs, such as using hysteroscopic adhesiolysis in combination with physical barriers, like biopolymers, as anti-adhesives. However, recent research shows that this approach is still associated with high recurrence rates and does not result in effective endometrial repair or improved reproductive outcomes, which is the primary goal of treatment. Another significant challenge is the high cost associated with using physical barriers in the management of IUAs. While human amnion, cell/hormone therapy, growth factors, and umbilical-cord-derived cells have demonstrated promising results in managing IUAs, they are not cost-effective, demand highly skilled professionals, and require long-term post-administration surveillance [73]. Hence, researchers and manufacturers should focus on producing affordable biomaterials

that can efficiently prevent or treat IUAs, ensuring that all patients, regardless of their socio-economic background, can access the treatment.

As mentioned earlier, although there are some limitations to HA hydrogels, such as rapid degradation by hyaluronidases, which reduces their residence time and bioavailability at the treatment site, increasing evidence from clinical trials suggests that combining hysteroscopic adhesiolysis with crosslinked HA hydrogels is a promising strategy for managing IUAs [42,55,57,111]. The importance of HA in biomedical applications, including tissue engineering, drug delivery, and reproductive medicine, has been emphasised in the literature [108]. However, Buckley et al. (2022) and Trucillo (2024) recommended that further research is necessary to fully explore the intracellular behaviours, biocompatibility, and regulatory considerations of this biomaterial to enhance its clinical effectiveness [3,59]. This is crucial because, although chemical crosslinking can improve the resistance of HA hydrogels to enzymatic degradation [89], it may also lead to increased hardness, which could cause a foreign body sensation and trigger inflammation or other adverse effects [58,199].

Thus, future studies should focus on finding the right balance in the degree of modification to preserve HA's biocompatibility and biodegradability [7], along with identifying and characterising the suitable carrier matrix that can be combined with HA to enhance its stability and sustained release. Building on the points discussed above, we suggest that chemically modifying HA through crosslinking and combining it with a well-defined, highly processable, and biocompatible biopolymer as a carrier matrix could address the current limitations of HA, enhance its therapeutic effects, and help bridge the existing gaps in managing IUAs. For instance, this could be accomplished by developing a minimally invasive solid dispersion device containing modified HA that can be implanted in the uterus to provide sustained release of the HA over a determined period of time. The implantable device must be designed to accommodate the wide variation in uterine sizes and shapes, as well as the specific characteristics and therapeutic outcomes of the implant. This approach could help prevent IUAs, promote the restoration of the endometrium after different types of damages, and enhance reproductive outcomes in women with IUAs.

Various engineering methods are currently utilised in the development of biomaterials and biomaterial-based products for biomedical purposes. Techniques such as HME, electrospinning, 3D and 4D printing play a crucial role in creating hydrogels, drug and growth factor delivery systems, cell-encapsulating membranes, biomaterial scaffolds, composite biopolymers, and the latest smart biopolymers. These innovations hold significant promise, especially in tissue regeneration, including endometrial repair. Moreover, by utilising organ-on-chip technology, endometrial organoids have recently been developed, using hydrogels combined with peptides and MSCs, that closely replicate the natural endometrial environment. These organoids not only promote internal tissue regeneration, providing valuable insights into the pathophysiology and underlying mechanisms of endometrial repair but can also support the effort toward personalised approaches in managing reproductive disorders including IUAs. Nonetheless, due to the intricate nature of the uterine physiological environment, careful consideration must be given to both the processing methods and resulting products to ensure not only the functional integrity of the biomaterials but also their short- and long-term safety for patients.

Finally, it has been noted that the pathophysiology of IUAs remains poorly understood, which might have potentially contributed to delays in developing effective treatments. Nonetheless, some research efforts are focused on uncovering the key mechanisms involved in the progression of IUAs. For example, by leveraging single-cell RNA sequencing technology, it was recently reported that the development of IUAs is marked by the loss of endometrial epithelium, disruptions in key signalling pathways like Wnt and Notch, and

the presence of secretory leukocyte protease inhibitor-expressing epithelium [21]. Additionally, another study showed that disrupted cell signalling and altered gene expression contribute to a dysfunctional environment that fosters fibrosis and inflammation while suppressing angiogenesis in patients with IUAs [22]. As a result, we advocate for further research into the molecular pathophysiology of IUAs to uncover relevant molecular insights related to novel disease mechanisms, identify specific biomarkers, and explore potential drug targets. These molecular biology insights could pave the way for the development of innovative therapies for this condition, which is placing a significant burden on both affected women and the field of reproductive medicine.

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