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The dura mater, the furthest and strongest layer of the meninges, is crucial for protecting the brain and spinal cord. Its biomechanical behavior is vital, as any alterations can compromise biological functions. In recent decades, interest in the dura mater has increased due to the need for hermetic closure of dural defects prompting the development of several substitutes. Collagen-based dural substitutes are common commercial options, but they lack the complex biological and structural elements of the native dura mater, impacting regeneration and potentially causing complications like wound/postoperative infection and cerebrospinal fluid leakage. To face this issue, recent tissue engineering approaches focus on creating biomimetic dura mater substitutes. The objective of this review is to discuss whether mimicking the mechanical properties of native tissue or ensuring high biocompatibility and bioactivity is more critical in developing effective dural substitutes, or if both aspects should be systematically linked. After a brief description of the properties and architecture of the native cranial dura, we describe the advantages and limitations of biomimetic dura mater substitutes to better understand their relevance. In particular, we consider biomechanical properties' impact on dura repair's effectiveness. Finally, the obstacles and perspectives for developing the ideal dural substitute are explored.

Impact Statement

Dura mater, a crucial protective membrane for the brain and spinal cord, often requires artificial substitutes when injured or removed. However, complications are still frequent (up to 40% of cerebrospinal fluid leakage) because substitutes lack the biological complexity and structural factors of native tissue, which affects its complete regeneration and function. This review discusses whether mimicking the mechanical properties of native tissue or ensuring high biocompatibility and bioactivity is more critical in developing an effective dural substitute. Overall, it can be assumed that mimicking the multiphasic structure could be more important than mimicking accurate biomechanical properties to achieve proper healing.

1. Introduction

The dura mater is the outermost connective tissue membrane that composes the tri-layered meninges and is a vital protection to the central nervous system (CNS).[1,2] Although dura mater is the thickest and most rigid of these membranes and plays the most important barrier role, it can be exposed to defects caused by a variety of factors, including tumor invasion, trauma, congenital abnormalities, iatrogenic causes (e.g. spinal cord surgery and lumbar puncture), and cerebrovascular diseases.[3,4] The presence of these defects could lead to cerebrospinal fluid (CSF) leakage and further complications, e.g. brain swelling, epilepsy, intracranial infection, meningitis, pseudomeningocele, or even spinal abscesses.[5,6]

In the last two decades, researchers' interest in this membrane has drastically increased (from approximately 5 to 40 papers per year according to the databases Scopus and PubMed) and the need for hermetic closure of dura defects prompted the development of several substitutes, whereas homologous options such as autografts and allografts are limited by the size of the dural defect (insufficient reachable graft to larger defects), additional operatory intervention, CSF leakage and in the case of allografts the quality of the graft, disease transmission, and foreign body reactions.[7–9] Sealants are another alternative to heal dura defects but are restricted to their size or shape. Also, some adverse reactions such as neurotoxicity induced by sealant have been reported.[10,11]

One of the primary requirements of biomaterials design is their mechanical properties. Tissues and organs are constantly subjected to various mechanical forces, including shear, stretching, compression, and a combination of these. As a result, a biomaterial should be designed to meet all of these requirements, comprising the intended tensile strength, elastic modulus, hardness, wear, fatigue resistance, and so on. For some tissues, including bone and dura mater, mechanical properties are indeed critical factors and can impair biological function.[12]

A recent review evaluated the properties and performance of several dural substitutes from different sources, including homologous, acellular, synthetic, and composite materials.[3] As established, an ideal dura mater substitute should not produce neurotoxicity, inflammatory or immunological reactions. Furthermore, the material should be tearing-resistant, absorbable, watertight, non-adherent to the surrounding tissue, and provide an architecture to the connective tissue that allows endogenous neodura development.[5]

Dural substitutes based on collagen are widely used among commercial synthetic alternatives. Still, most of them lack the complex biological and structural factors of the dura mater's hierarchical structure, which affects its complete regeneration and function and could also result in incomplete healing, resulting in wound/postoperative infection and some cases CSF leakage.[3,13,14]

To face this issue, not only in dural defects but also in other areas of tissue engineering, the latest tissue substitute approaches focus on creating a bioinspired, or biomimetic, cell environment that recreates the natural gradients in extracellular matrix (ECM), tissue topology, cell distribution, and biomechanical properties.[15–18]

Considering the mechanical properties, the biomimetic approach, and the biocompatibility requirements, it is complex to identify which factor should be considered as the key to developing an efficient substitute (Fig. 1): being accurate in terms of mechanical properties (i.e. mimicking the properties of the native tissue) or being biologically reliable (high biocompatibility and bioactivity)? Or are both aspects systematically linked in successful dura substitutes? In addition, the established dura mater mechanical properties values usually consider it as a bulk, although the dura mater itself is often described as a multilayered structure.[4] In this context, when would a substitute be biomimetic enough? If mechanical values vary according to the fibrous structure of each layer of the dura mater, should the mechanical properties be considered as a whole or for each individual layer? With the lack of uniformity regarding the number of layers of dura mater to produce a substitute, would the mechanical values be closer to the physiological scenario if they were analyzed layer by layer?

The objective of the present paper is, therefore, to discuss specifically these questions, rather than to present a complete overview of dura substitutes, as it has been done recently.[3,19,20] After a brief description of the properties and architecture of the native cranial dura, we will describe the advantages and limitations of biomimetic dura mater substitutes to understand their relevance better. In particular, we will consider how biomechanical

properties impact the effectiveness of dura repair. Finally, the challenges and perspectives for developing the ideal dural substitute will be explored.

2. Methodology

A systematic selection of peer-reviewed articles within the thematic research areas of "dura mater substitute" or "dural mechanical properties" published from 1965 until July 2023 was defined. The online databases used were PubMed, ScienceDirect, and Scopus, leading to around 500 occurrences.

Only peer-reviewed studies in the English language were considered. Studies involving homologous and acellular materials for dura substitutes, as well as dural sealants, were excluded. The spinal dura substitutes were also excluded from this review due to the scarcity of spinal dura studies, particularly concerning mechanical properties. There was no statistical comparison between the spinal and cranial dura mater, which hampered the identification of accurate mechanical values.[20]

To better understand the role of mechanical properties in the efficacy of cranial dura mater artificial substitutes, only studies that provided mechanical information were chosen, resulting in a selection of fewer than 30 articles to investigate.

3. Anatomy of dura mater

Dura mater, or pachymeninx (pachy meaning thick in Greek), is the furthest and strongest membranous layer that composes the three meninges. Composed of a complex triple-layered membrane structure, the meninges support and protect the constituents of the central nervous system.[21]

These protective layers surround the brain and spinal cord, preventing them from shifting position when the head and body move. They also enclose the cerebrospinal fluid, which aids in the absorption of external shocks and the prevention of CNS traumas (Fig. 2). The meninges, which include both the cranial and the spinal meninges, are constituted of not only connective tissue but also walls of blood vessels and the sheaths of nerves. The other two layers are called arachnoid and pia mater.[22]

The arachnoid mater, named after its similarity to a spider web, is a fibrous, thin, and avascular membrane located below the dura, specifically below the dura border cell layer.

It is followed by the pia mater (meaning "tender matter"), the innermost layer, which is a very thin and capillary-rich membrane attached to the brain that coves all the external surfaces of the CNS and penetrates the sulci and fissures. Between the arachnoid and pia mater is a space known as "the subarachnoid space", which is filled with CSF and contains blood

vessels as well as the arachnoid trabeculae's fibers and cells. Cerebral veins and arteries enveloped by pia mater are also present.[21,23]

Recently, an interesting article revealed the existence of a fourth meningeal layer designated as the subarachnoid lymphatic-like membrane (SLYM). The SLYM divides the subarachnoid space into two compartments, acting as a barrier, and is morpho- and immunophenotypically analogous to the mesothelial membrane present in organs and body cavities.[24]

The dura mater is close to the inner surface of the bone and is tightly attached to the neurocranium, from the cranial vault to the skull base, reaching the foramen magnum.[4] At the foramen magnum, the dura divides into an external layer, the periosteum of the spinal canal, and an internal layer that creates the folds of the dura mater.

Among each layer, a gap appears to prevent adhesion and absorb shock waves against head trauma. This gap between the dura mater and arachnoid is filled with a lubricant fluid, whereas between the arachnoid and pia mater is filled with lymphlike cerebral spinal fluid.[4,25,26]

Vandenabeele et al.[1] revealed three different layers in the dura (Fig. 3) using an *in situ* perfusion fixation approach immediately postmortem (in the case of spinal samples here), which are mostly constituted of fibroblasts, extensive amounts of extracellular collagen, microfibrils, and elastic fibers. This collagen matrix is formed substantially from collagen type I, although collagen types II and III are also present.[27,28] Dural fibroblasts are elongated cells mainly oriented parallel to the flat axis of the dura mater and their cytoplasm contains rough endoplasmic reticulum, mitochondria, ribosome, Golgi apparatus, filaments, microtubules, a flattened dense nucleus, and some vesicles at their membrane surface. Also, as a highly innervated tissue, the dura contains most of the meningeal lymphatic vessels when compared to the other layers.[29]

The peripheral part of the dura (designated as the "outer dural border layer" or the "periosteal dura layer") is adherent to the periosteum and the base of the skull and composed of non-arranged extracellular collagen as well as long parallel cellular extensions of dural fibroblasts, osteoblasts, and elastic fibers. This layer has a thickness of around 2 μm and a tough structure due to the large amount of collagen.[30]

Then, the inner layer is predominantly constituted by extracellular collagen and high vascularization, within a higher density of dural lymphatics, responsible for CSF and CNS-derived macromolecules drainage into the cervical lymph nodes. This layer, also known as the

"fibrous dura" or the "meningeal dura layer", varies in thickness depending on whether it is located in the cranial or spinal areas.

The middle layer is followed by the "dura border cell layer", and the transition could be clearly distinguished by an abrupt decrease in collagen and an increase in extracellular spaces filled with amorphous granular material and densely packed fibroblast cells. This layer has a thickness of approximately 8 μm and is firmly attached to the arachnoid trabeculae. Elastic fibers are consistently absent, and a thin layer of dural fibroblasts seems to adopt a specific, elongated phenotype known as "dural border cells". These fibroblasts appear undulated and tightly packed.[1,31–33]

Furthermore, an alternative dura mater structure has been discussed in the literature. In 2011, Protasoni et al.[4] published research where they could distinguish not three, but five layers of dura mater. By scanning electron microscopy, the authors recognized the outermost layer, the dura border cells layer, and instead of one middle layer, they identified three layers due to the diverse arrangement of collagen fibers in different directions, known as the external, vascular, and internal layers.

4. Mechanical properties of native cranial dura mater

As previously stated, the dura mater is mainly made up of fibers, so the ultimate strength, elastic modulus, and stiffness of the entire tissue are related to the type and volume fraction of these fibers. Fiber orientation defines behavior as anisotropic or isotropic[35,36] and previous investigations considered dura as structurally isotropic, although further research suggested that mechanical tests conducted on large samples masked the local anisotropic behavior.[37] Thereafter, the cranial dura mater demonstrates complex anisotropic morphology, with area dependent on mechanical properties.[38]

Viscoelasticity is an intrinsic tissue property and is related to the material time-dependency anelastic behavior, which means there is a loss of energy inside the material, retarding the response to a stimulus.[39] Unlike several soft tissues that have elastic properties and obey Hooke's Law, where displacement is directly proportional to the force applied, the tissues of the head cannot be described in the same way. The time-dependency property configures one of the mechanical responses from head tissues and has been studied by several researchers.[40–46] The dura mater can be properly classified as a linear viscoelastic material because it does not significantly deform by stress level during creep testing.[46] The viscoelasticity of the dura mater is caused by its ground substance, which absorbs a variety of mechanical forces. When some force is applied to the membrane, the load is transferred from

fiber to fiber and lubricated as they move in opposite directions. As the fibers move, the geometry rearranges, and the viscous ground substance inhibits, acting as an opposition charge, the external force.[47]

Collagen is a protein with a high Young's modulus (100-1000 MPa) and a fundamental structural element acting as a load-bearing in soft tissues.[48] Its presence as a compact and dense structure in the human dura mater provides high tissue modulus, high tensile strength, and resilience for this membrane.[49] Higher mechanical properties, such as tensile strength, promote intracranial pressure resistance and are essential for positioning or repositioning the substitute during surgical procedures.

Being the most rigid layer, dura mater's biomechanical behavior is a critical factor that could compromise biological functioning if altered.[12] Recently, an elucidative and extensive literature review of the mechanical properties of the native dura mater was conducted.[20] The authors reviewed 400 studies, 13 of which were eligible for analysis, and concluded that Young's modulus (n = 448), ultimate tensile strength (n = 448), and strain at maximum force (n = 431) for native cranial dura mater were 68.1 MPa, 7.3 MPa, and 14.4% respectively. Although initially highlighted to be used in numerical models, these values could become targets for novel dura substitutes claiming to be biomimetic. Even though the authors did not discuss the values related to the strain at break, several researchers reported the value of 116 ± 3% as the reference for human dura mater (Fig. 4).[50–52] For this review, it was decided to prioritize elongation at break over elongation at maximum force because the majority of the publications selected provided information about this property.

Moreover, given the predominant method for measuring biomechanical properties, it is important to note that the current values consider dura mater as a whole, rather than as a multilayer structure with various intermediate mechanical properties. This choice will be discussed further in the present review.

A mean thickness of 0.322 mm with variability about the intracranial location was revealed through histological and anatomical structure analysis of the dura mater.[53] Some authors showed that the dura mater thickens with age, increasing from 0.3 to 0.8 mm.[54–57] Oppositely, Fam et al.[58] reported a decrease in dura mater with age. Other authors suggested that the thickness of the dura mater may vary site-dependently rather than with age.[59] It was also reported that mechanical properties such as elastic modulus, maximum strain, and ultimate tensile strength could decrease with age but not significantly with gender.

5. Cranial dura mater artificial substitutes

The ultimate goal of biomaterials is to develop materials that combine mechanical, physicochemical, and biological attributes in order to mimic the tissue, organ, or body function.

As previously mentioned, an ideal dura mater substitute should not produce neurotoxicity or immune reactions. Also, the material should provide an architecture for neodura development and promote the adherence and migration of dural fibroblasts from the substitute's periphery to the core.[60] The prevention of CSF leakage is another point to be considered, and the suturing procedure may be evaluated to avoid potential risks that lead to leakage.

Synthetic and natural polymers have been used to fabricate dural substitutes due to their capability to prevent further interventions, thereby avoiding the risk of infections,[3,61,62] as well as avoiding the risk of transmitting diseases (which could appear with autologous, allograft, or biological materials). Another advantage is that polymers can be easily processed into different structures, formats, and sizes. Several techniques have been used to produce artificial substitutes, such as electrospinning (see below),[14,60,63–65] solvent casting,[66,67] hot press molding,[68] compression,[61] polymerization,[69] etc.

Table 1 summarizes the information retrieved from previous studies on the processing technique, mechanical properties, number of layers, watertightness, and the biomimetic claim of cranial dura mater substitutes produced until July 2023, highlighting specific considerations relevant to the objectives of this review.

There are several approaches for developing a scaffold, including mimicking the structure, components, mechanical properties, biological properties, or even a combination of those from native tissue. As a result, some researchers decided to replicate the various dura mater layers, resulting in triple-, double- or single-layer substitutes (Fig. 5).

Indeed, multiphasic scaffolds are one of the latest approaches in tissue engineering, allowing to mimic complex structures by incorporating multiple phases or layers, each serving a specific purpose to promote tissue integration and regeneration. They are being investigated for various applications, including bone regeneration, cartilage repair, tendon repair, periodontal regeneration, etc.[70–73] In particular, an important focus on developing interface tissues has increased the search for such scaffolds, and several studies on osteochondral regeneration have reported the advantage of using biomaterials with more than two layers because of their ability to replicate the structure and composition, comprising the gradient between the cartilage zones, calcified cartilage, and subchondral bone.[74,75] The possibility of associating different phases with varying properties, such as mechanical strength, porosity,

and degradation rates, offers several advantages to emulate with a higher degree of similarity the physiology and function of the tissue, enhancing cell-material interactions and improving integration with the surrounding tissues. As dura mater is natively a multiphasic structure and an interfacial tissue between bone and central nervous system, it appeared relevant to sort the different approaches reviewed here based on the number of layers considered.

5.1. Triple-layer

Triple-layered scaffolds were developed to recreate the original structure of native dura mater, as inspired by its outer, meningeal, and border layers. This biomimetic approach can mimic morphological, mechanical, and/or biological properties.

Electrospinning is one of the most employed techniques to fabricate and modify scaffolds in tissue engineering. This technique involves electrically charging a material solution to form a jet to create fibers. The discharged solution is attracted by a collector (negatively charged or grounded), which forms an elongated jet as the solvent evaporates and the jet solidifies.[77–79]

The benefit of this technique is the ability to obtain fibers from varied polymers and composites with diameters ranging from nano to microscale, resulting in mats with high surface area, porosity, and mechanical properties, as well as the ability to mimic the extracellular matrix structure in terms of composition and morphology.[15,80,81] Electrospun membranes with oriented fibers have gained popularity due to their ability to influence cell alignment and processes, as previous studies have demonstrated.[60,82–89]

Of these advantages, many researchers implement electrospinning because of its versatility in producing dura mater substitutes with one or more different layers. Recently, a mini-review described the current state of electrospun dura mater substitutes.[19] Furthermore, it was demonstrated in the case of poly (L-lactic acid, PLLA), the possibility of creating a hydrophobic surface by applying high voltage during electrospinning, which could improve the watertight property.[90]

A multilayer electrospun nanofibers scaffold was developed by Wang et al.[76] to be used as a biomimetic dural substitute (Fig. 5a). In their work, three layers were fabricated and assembled using electrospinning: an inner layer of polylactic acid (PLA) to reduce tissue adhesion, a middle layer of polylactic acid and polycaprolactone (PCL) to promote mechanical strength and impermeability, and an outer layer of collagen type I and PLA to increase tissue regeneration and promote mechanical strength, respectively. Mechanical tests revealed that the multilayer scaffold presented strength values similar to the native dura and

an elongation at break over 80%. The scaffold's high tensile strength allowed for suturing without causing cerebrospinal fluid leakage. After one month of implantation, there was no evident inflammation in the brain tissue, and it was observed the formation of collagen fibers on the scaffold, fibration in the surrounding tissues, migration of peripheral cells into the scaffold's outer layer, and no brain tissue adhesion to the scaffold's inner layer. The authors thus demonstrated the possibility of mimicking mechanical and biological layer properties. However, no information was available about the scaffold's non-toxicity and physiochemical properties after a long period, as well as the absence of CSF leakage.

Another three-layer structure was designed by Liao et al.[91] to mimic the structure and components of native dura mater. Physical winding was used to combine an electrospun PLLA film with another electrospun chitosan/PLLA film. The electrospun composite was then coated with a microporous hydrogel layer made of gelatin, chitosan, and small intestinal submucosa (SIS). The findings showed prominent flexibility to an appropriate suture, satisfactory structural stability after implantation, and a good biological response such as tissue regeneration due to the hydrogel's bioactivity, anti-adhesion property, collagen deposition, and angiogenesis, with no significant inflammatory response.

Unlike previous studies, this structure lacked the dura mater's tensile strength and elongation at break. Despite the lower values compared to native tissue, the authors justified that the maximum tensile required to maintain CSF pressure is approximately 6.66 KPa (50 mmHg). Intracranial pressure is about 5 mmHg, but it can rise to 50 mmHg when coughing or sneezing.[92] Furthermore, pressureless drop penetration and fluorescent dye penetration tests revealed excellent leakproof results.

In 1997, researchers developed a triple-layer dural substitute.[61] In their work, a polyglycolic acid (PGA) nonwoven fabric was placed between two L-lactic acid-ϵ-caprolactone copolymer films. The composite was fabricated by heat compression and rapid cooling, and it showed a low elastic modulus but tensile strength comparable to the native dura, allowing it to resist intracranial pressure and prevent CSF leakage in a rabbit model after 5 weeks of implantation. The substitute was absorbed 24 weeks after surgery, and the dura-like tissue was completely regenerated, with no inflammatory cells, well-oriented collagen fibers, and capillary neovessels present in the dural defect.

A three-layered structure of different bioabsorbable polymers was designed in order to achieve a watertight dural substitute.[68] Ring-opening polymerization was used to create several ternary copolymers from L-lactide, glycolide, and ε -caprolactone. The appropriate composite was selected based on *in vitro* leakage tests. Each copolymer layer had a thickness

of 100 μm and was fabricated using the hot press molding process, with the central layer viscoelastic and the exteriors elastic. The elastic modulus and bending resistance of the elastic materials were evaluated following leakage tests in which the samples were sutured together. It was found that when Young's modulus was less than 10 MPa, significant leakage was observed. For bending resistance, significant leakage occurred in samples with values greater than 340 mN.mm.

5.2. Dual-layer

Among the options for mimicking tissue structure, some researchers decided to reproduce two layers of the dura mater instead of three, with each layer designed to perform a specific function such as regeneration, watertightness, or mechanical property.

Flanagan et al.[6] created biomimetic bilayer substitutes with good mechanical properties and hydrophobic behavior, but they observed that pinholes formed by suturing reduced the water tightness response.[93,94] To prevent this issue, a sutureless dural bilayer substitute was proposed to mimic the dura's microenvironment, with one layer made of nonporous silk fibroin film with an adhesive layer of electrogelated silk and the second layer of electrospun silk/ polyethylene oxide (PEO) to promote tissue regeneration (Fig. 5b). Silk fibroin, a versatile biomaterial, has been successfully used as a scaffold due to its high biocompatibility and mechanical strength.[95] Moreover, an adhesive gel from silk fibroin could be obtained using an electrogelated technique, which consists of transforming an aqueous solution into a gel via an electric current.[96]

The composite showed Young's modulus between 7.16 and 12.1 MPa and the tensile strength values ranging from 0.88 to 1.53 MPa. During their study, the authors compared the elastic modulus of their composite dual layer to a value of the native dura mater that is no longer considered, 2.75 MPa rather than 68.1 MPa.[20] Nonetheless, burst tests were performed to assess the membrane's capacity to prevent CSF leakage, and it was able to withstand a burst pressure of 205 mmHg, which is four times higher than the maximum intracranial pressure. Besides, only *in vitro* tests were conducted, and given the low Young's modulus values, the extent of these properties for *in vivo* tests remains unknown.

Electrospun scaffolds were used again for two-layer approaches. Aligned nanofibers were used to develop the structure of one side of a bilayer dural substitute, while the other side was constituted of random nanofibers.[97] The biomimetic dural substitute was composed of biodegradable poly (DL-lactide-co-ε-caprolactone, PLCL), poly (propylene glycol, PPG), and sodium acetate blend electrospun nanofibers with a thickness of 130 μm. Tensile tests were

performed with loads oriented parallel and orthogonal to the fiber alignment anisotropic mechanical properties. *In vivo* tests demonstrated that aligned fibers enhanced cellular direction into the durotomy region, allowing for a more efficient dural healing response than random nanofibers. According to the author's hypothesis, aligned fibers induced new tissue infiltration from the wound's edges faster than random fibers. The dura substitute promoted little or no inflammation response after 28 days, and no CSF leakage was observed.

Two bilayer dura substitutes were prepared to mimic one dense layer to act as a barrier against CSF leakage and brain adhesion and another layer with a porous surface to promote tissue regeneration.[98] The dense layer was obtained by solvent casting composed of chitosan and bacterial cellulose (BC). In contrast, the porous layer was divided into two groups: one composed of BC and O-carboxymethyl chitin (O-CMCH) crosslinked with glutaraldehyde (GA), and the second one composed of BC and O-CMCH crosslinked with citric acid (CA). Porous layers were obtained by preparing a gel from suspension and then lyophilizing it. BC was added in both layers to enhance mechanical properties. In a pressure simulation test, the two bilayer dura candidates overlapped 6 times the intracranial pressure (900 mmHg) for 30 min without leakage. Both dual layers showed tensile strength over the 7.3 MPa (reference value as stated by Percy et al.[20]) in a dry state (GA = 11.71 MPa and CA = 17.64 MPa), but when tested in a wet condition, only the sample crosslinked with GA achieved the expected value (7.98 MPa). Moreover, the glutaraldehyde layer had higher porosity (pore sizes ranging from 90 to 200 μm) and higher porous connectivity compared to the citric acid crosslinked layer. After 17 days, abdominal implants showed good anti-adhesive properties, no cytotoxicity, and induced cellular proliferation. However, additional *in vivo* test is needed to determine the barrier's ability to prevent CSF leakage.

5.3. One-layer

Monolayer substitutes are the most common alternative that has been explored by researchers. The ability to obtain a material with multiple properties in a single layer is a versatile option for achieving the envisaged performance.

One example is Neodura™, an absorbable composite of PLLA and porcine gelatin produced in a fleece-like structure, serving as a monolayer biomimetic dural substitute.[99] The composite's mechanical and biological properties were compared to the commercial substitute DuraGen™ (collagen-based). Unlike the collagen substitute, which showed very fragile behavior in mechanical tests, the composite substitute demonstrated an average tensile strength of 3.8 ± 0.34 MPa and an average elongation at break of 84.87 ± 8.45%, which were

slightly lower than the expected (7.3 MPa and 116%). However, both patches provided good cytocompatibility and an appropriate growth environment. Furthermore, the cells on the composite patch were firmly attached and presented a flat form with affluent pseudopodia supporting migration, whereas the cells on collagen showed inferior migration ability and a polygonal or fusiform aspect. Also, during the *in vivo* experiments, it was found that, despite the low mechanical properties, the enhanced strength of the composite patch resulted in superior resistance to increased intracranial pressure compared to collagen by improving the tensile strength of repaired tissue.

Another study compared commercial dura substitutes to a one-layer biomimetic absorbable substitute developed by Medprin Biotech GmbH.[13] This biomimetic substitute was constituted of PLLA fibers, which recreated a structure capable of facilitating cell migration due to their porosity (Fig. 5c). PLLA fibers were deposited layer by layer to form a fleece-like structure using an electronically controlled procedure. The membrane with a thickness of around 0.3 mm presented fibers with an average diameter of 0.7 to 2 μm and interconnected pores. Tensile strength did not differ significantly between transverse and longitudinal directions, ranging from 2.8 to 4.3 MPa. When both directions were combined, the biomimetic patch had an average tensile strength of 4.14 ± 0.18 MPa, which was slightly lower than the native tissue. Nonetheless, it allowed for a complete suture without CSF leakage.

In vivo comparisons with commercial biological (NormalGEN) and synthetic (SEAMDURA) alternatives were conducted, and the results showed no significant difference between commercial substitutes and the biomimetic patch in terms of tissue biocompatibility, inflammatory response, and CSF leakage. After 90 days, biomimetic and synthetic substitutes demonstrated no tissue adhesion, whereas the biological substitute adhered to the cortex. The same response was found for neovascularization and fibroblast infiltration, in which synthetic and biomimetic patches were wrapped in new tissue and replaced with connective dura-like tissue. These biological processes were not demonstrated by NormalGEN. After 2 years, all patches presented safe and effective dural healing. Despite this, the biomimetic substitute was completely degraded and replaced with new dural tissue. SEAMDURA's material was nearly depleted. NormalGEN degraded slowly and produced few focal calcifications. SEAMDURA's material was nearly depleted. A clinical study was conducted, and there was no evidence of CSF leakage or local infection. Furthermore, after 2 years of implantation, the patient showed normal functional capacities.

By mimicking the fibrous structure of dura mater, Chuan et al.[50] created a single-layer electrospun scaffold of poly (D-lactic acid) with grafted-tetracalcium phosphate (g-TTCP). The scaffold exhibited thermal stability and mechanical properties similar to native tissue. *In vitro* results indicated good compatibility and no cytotoxicity. In terms of biological results and mechanical properties, this substitute appeared therefore a good alternative, but *in vivo* studies need to be conducted.

A transparent silk fibroin-based artificial dura mater with a tensile strength of 65.6 ± 7.1 MPa and an elongation at break of 7.0 ± 0.6% was created via solvent casting.[66] Even though these results differed significantly from the native tissue, the high tensile strength allows sutures to be performed without tearing. Furthermore, the transparency allowed for better visualization during operation, and the membrane demonstrated no CSF leakage and prevented inflammation after two weeks of implantation. Researchers emphasized the necessity of testing the dura substitute in large animals over a longer period.

Wang et al.[100] developed a monolayer bioactive nanofiber dura substitute with a controlled release of insulin-like growth factor 1 (IGF-1). In comparison to native tissue, PCL nanofibers encapsulated with hyaluronic acid methacryloyl (HAMA) and IGF-1 demonstrated high tensile strength (over 99 MPa) and lower elongation at break (around 56%). Furthermore, the substitute could provide structural support during the *in vitro* degradation process and long-term release of IGF-1, thereby promoting neural cell survival. However, *in vivo* studies are required to determine whether this high-toughness substitute is adequate to prevent CSF leaks.

A synthetic substitute was proposed by designing a polysaccharide-based hydrogel film with mechanical properties that outperformed the majority of biopolymer-based hydrogels.[51] The authors prepared the hydrogels by complexing oppositely charged *k*-carrageenan (*k*-CG) and chitosan at varying concentrations, then evaporated the solutions and swelled the films to achieve an equilibrium state. The combination of ionic bonds between both polymers, as well as hydrogen bonds between *k*-CG, allowed the samples to have tensile strength and an elongation at break comparable to native dura mater. Furthermore, the gel films exhibited good self-recovery after the cyclic loading test, as well as anti-adhesion properties, which could be attributed to the hydration layer that prevents protein adsorption and cell attachment. Despite the favorable results, no CSF leakage or *in vivo* tests were conducted.

Huang et al.[101] recently developed a composite hydrogel with anti-adhesive properties to use as a dural substitute. A hyaluronic acid (HA)/carboxymethyl cellulose (CMC) hydrogel was created *in situ* at the surgical site by co-crosslinking with 400 nm visible light the

compounds of HAMA and carboxymethyl cellulose methacrylate (CMCMA). After 3 days, the composite's weight decreased by 70%, according to the degree of degradation assessed. Compression tests were performed, and the hydrogel had Young's Modulus, compressive stress to failure, and compressive strain to failure values of 0.12 to 0.82 MPa, 0.20 MPa, and 39%, respectively. *In vivo* studies demonstrated that the hydrogel could be used as a dural substitute to prevent adhesion after craniotomy by reducing fibroblast penetration and migration, indicating an effective approach to adhesion reduction. No mention of preventing CSF leakage was stated. Although this material could be considered a sealant, it was included in this review because the authors described it as a dural substitute.

6. Synthesis and discussion

Based on the variety of elements that a dura mater substitute should have and the requirements that it must meet, biomechanical properties are paramount to mimicking the original tissue.[103] The ability to allow a proper closure to avoid CSF leakage, the most common complication in neurosurgery, to maintain intracranial pressure, and to protect the brain from external forces is mandatory,[3] and all of these attributes depend on the biomechanical properties of the biomaterial.

Even though numerous biomaterials have been created to repair dura mater, the majority lack the hierarchical structural characteristics of dura mater.[14] To avoid dural defects and/or complications post-duraplasty, researchers began to recreate, or mimic, the native tissue.

The goal of mimicking the three layers is to achieve a substitute that will not only act as a patch to close the defect, but will also restore the dura's functions, involving all of its complexity and multifunctionality, allowing the surrounding tissues to adhere, proliferate, and vascularize onto this material, providing the functions and particularity of each layer, such as mechanical support, adhesion, fluid leakage prevention, and even therapeutic drugs release. Interestingly, synthetic biomimetic dura substitutes that mimic these different layers of the dura mater do not exhibit the expected mechanical values when compared to native tissue, such as an elastic modulus of 2.7 MPa or elongation at break ranging from 63% to 80%.[76,91] Fig. 6 depicts an overview of the mechanical properties of the substitutes with one, two, and three layers described in Table 1 as compared to the native dura mater. No substitute with two or three layers reaches the expected value for elastic modulus (Figs. 6a and 6b). When compared to the dura mater's tensile strength (Figs. 6c and 6d), the majority of the substitutes from various groups met the predicted 7.3 Mpa value. Furthermore, almost all substitutes ruptured before attaining the reported 16% expansion for the native tissue (Fig. 6e).

Liao et al.,[91] using a dura defect simulation finite elements model, demonstrated that the maximum strength and strain at maximum force needed for the dura mater to sustain the maximum CSF pressure (6.66 KPa, or 50 mmHg) would be 0.197 MPa and 0.05%, respectively. Thus, the values obtained by its multilayer substitute (366 KPa and 63%, tensile strength and maximum strain, respectively) are justified. Another factor mentioned by the authors is that one of their composite's layers acts as an antileakage barrier due to its hydrophobic property, which is a fundamental feature of dural substitutes.

According to this perspective, native mechanical properties are not a specific value to target, but rather a threshold, a minimum level to meet in order to avoid failure. This contrasts with bone substitutes, for instance, which are well known to avoid both lower and higher stiffness.[111]

Conversely, in the other two cases of three-layered but non-biomimetic substitutes, the purpose of creating three layers was to obtain mechanical properties similar to the natural tissue and an appropriate degradation rate for the formation of a new dura tissue. Authors who developed the composite of a viscoelastic layer between two elastic layers claimed that for the elastic layer, the maximum value of Young's modulus should be greater than 10 MPa. It would prevent the suture holes from expanding and changing size, thus preventing CSF leaking. Another important aspect that the authors highlighted was bending resistance, where they demonstrated that very high values (over 340 mN.mm) resulted in a considerable leak volume. As a result, they obtained a composite with a 15 MPa elastic layer (Young's modulus), which is 4 times lower than the native tissue, and a bending resistance of 200 mN.mm.[68]

As previously discussed, the advantage of creating a composite that mimics three or two layers instead of one layer is the ability to tailor multiple functionalities in each layer by optimizing mechanical properties and designing distinct mechanical characteristics such as tensile strength, flexibility, or elasticity, thereby providing enhanced support and resistance to mechanical stresses. In addition, including a layer with hydrophobic or impermeable characteristics might improve watertightness, reducing the risks of fluid leakage.

Following this goal, researchers designed composites with two layers, one promoting cell adhesion and tissue regeneration and the second providing watertightness to the substitute. This extra layer could be a hydrophobic material or composite,[6,93,94] a dense layer,[94,98] or obtained by combining material and fiber alignment.[97]

Fiber alignment is an alternative method for mimicking and optimizing mechanical properties via orienting the fibers in a specified direction, such as parallel or orthogonal to the

applied forces, resulting in improved tensile strength, stiffness, and load-bearing capacity. Also, this nanotopography induces cell orientation, and there was a significant variation in cellular response when using random or aligned oriented fibers, which could suggest enhanced cell migration during wound healing.[112] The bilayered substitute produced by Kurpinski and Patel[97] achieved the expected ultimate strength thanks to the fiber alignment and exhibited improved tissue healing after one month of implantation when the aligned fibers were placed directly into the injured site. Despite the encouraging results, the authors recommend a longer period of implantation to verify its suitability against CSF leakage.

Nonetheless, these multilayer patches showed a satisfactory biological response, allowing cell adhesion and migration, absence of CSF leakage, no local infection, and wound healing. The limitation of most of these substitutes is that *in vivo* studies must be performed or pursued for a longer period, as well as clinical exploration to validate the models. Unfortunately, most, if not all, of the biomaterials discussed here face this challenge. Besides this limitation, these findings suggest that an overall biomimetic, multiphasic structure could dismiss the need for highly biomimetic mechanical properties. Apparently, the following characteristics, such as fiber alignment, watertightness, or the ability to prevent fibrosis, appear to stimulate a physiological response that inherently guides the restoration of dura functions, which may be more important than accurate Young's modulus or elongation at break values. Indeed, in substitutes with two or more layers whose mechanical property values did not reach those of natural tissue, it was possible to observe that the substitute nonetheless fulfilled some dura functions when tested by *in vitro*, physically, and in some cases *in vivo*.[6,68,97]

However, it is important to point out that the mechanical values used as a reference consider dura mater as a whole, rather than as a complex multilayer structure that has various intermediate mechanical properties. Moreover, the lack of uniformity in the number of layers, as well as the influence of age, sex, and the site-dependency, hampered a comprehensive knowledge of dura mater. All of these factors could potentially clarify why some substitutes displayed efficacy even while having differing mechanical properties.

One common element among all substitutes, regardless of whether they claim to be biomimetic or not, is the will to prevent CSF leakage in the long term. To achieve this, some aspects should be avoided, including holes or cracks during suturing, hydrophilicity behavior, and a mismatch between tissue regeneration and material degradation rate. Another factor to consider is that the majority of the studies used quasi-static velocities or room temperature tests to determine the mechanical properties of their substitutes, which may not be representative of the real-world situation to which the human head would be subjected, such

as impacts and injuries caused by accidents like falls, contact sports, etc. Dynamic and multiaxial loading analyses are more likely to simulate the forces of a head impact, as well as appropriate temperature/medium conditions during tests.[113] These analyses must be scrutinized to identify the real biomechanical properties of dura mater. In this literature review, only a few researchers evaluated their substitutes using corporal temperature conditions or cycle loading tests. Indeed, it could be challenging to perform an accurate comparison with native properties since no dura mater value has been established for different analysis conditions (i.e. dynamic, multiaxial loading test, body temperature, etc). Yu and coworkers[51] demonstrated that their scaffold presented a good biomechanical stability after cycling test (Figs. 7a and 7b), despite having a lower Young's modulus and tensile strength than the native tissue (1.2-25 MPa and 2-6.7 MPa, respectively), whereas Kizmazoglu et al.[103] performed mechanical tensile tests at 37 °C in saline solution.

Kunze et al.[109] provide another example of the difficulty it could be to define an optimal mechanical value. They fabricated one-layer dural patches with different compositions that had elastic modulus of 1260 and 660 MPa; tensile strength of 20.3 and 10.1 MPa; and elongation at break of 6.4 and 10.9%, respectively. Regardless of their high stiffness and low flexibility compared to the native dura mater, the patches showed good stability, with no inflammation or adhesion between the patch and the brain or dura mater after 9 months of implantation.

Regarding the other examples of one-layer substitutes, most of them did not mention the elastic modulus (Table 1), and of those that did, at least half of them had a lower value than the native tissue. However, these substitutes exhibited satisfactory *in vivo* response and, in some works, positive clinical results, including wound healing and the absence of CSF leakage and local infection (Fig. 7c).[13,99]

In summary, the substitutes exhibiting the expected biological response displayed mechanical properties that diverged from the values established for the human dura mater.

Several gaps in this literature review were identified concerning dura mater mechanical values and the relationship between properties and substitute efficacy. It remains unclear and an open question since there is an extensive lack of individual biomechanical properties for each layer, taking into consideration factors such as the influence of age, sex, and site-dependency, as well as the role of vascular and avascular areas in dura mater strength. It is not possible to assume that these values are completely reliable. They could serve as a basis for developing new substitutes, but maybe not as strict exclusion criteria.

Indeed, a thorough investigation of each individual dura mater layer's intrinsic mechanical properties should be performed. There is also a need to develop a unique protocol for performing mechanical tests that are more accurate and representative of the real forces that the head is subjected to, such as dynamic and multiaxial tests, in order to obtain a full understanding of the nature of this tissue. In fact, the strategy of mimicking some dura mater structure properties such as aligned fibers, watertightness, and adhesiveness appears to be a promising approach for stimulating the physiological response of dura functions.

Despite this gap between synthetic substitutes and native dura mater, recent advances in material science, including the use of nanotechnology and biofabrication techniques, offer favorable prospects. Tailoring biomaterial compositions, optimizing structural designs, and incorporating bioactive components such as bioactive molecules, growth factors, and stem cell-based therapies, hold potential for enhancing biomechanical properties and promoting tissue regeneration. Personalized medicine could also help face the variability of dura properties between individuals, but the most common fabrication techniques for such approaches (namely 3D printing) are not commonly investigated in the context of this tissue.

Afterward, it is essential to recognize the intricacies of the CNS environment and further studies should explore the role of biomimetic substitutes in the physiology of the dura mater, investigating whether some anatomical aspects like blood supply, lymphatic drainage, macrophage migration, and others could be mimicked in a substitute. Long-term *in vivo* studies are imperative to assess the biocompatibility and efficacy of dura substitutes in real-life scenarios, ensuring safe and successful outcomes for patients with dural lesions.

Lastly, while attempts to mimic the biomechanical properties of the native dura mater remain ongoing, it is through a comprehensive understanding of tissue mechanics, innovative engineering approaches, and interdisciplinary collaboration that will ultimately be possible to strive toward developing clinically viable substitutes that approximate the effectiveness and functionality of the natural tissue.

7. Conclusion

In summary, based on the findings of the substitutes discussed in the present paper, it is not possible to conclude whether structural biomimicry without the ideal mechanical values would be sufficient to become a good dural substitute candidate, particularly given the lack of long-term in vivo tests and clinical trials. However, unlike other tissues, most of the biomechanical properties of the native dura mater may be thresholds to reach rather than exact values to target with high accuracy. In addition, it is not always stated what an optimal dural

substitute should do: while preventing CSF leakage and epidural fibrosis are often the main objectives, some studies investigated more advanced properties (such as neovascularization and suture considerations). Overall, it can be stated that a biomimetic, multiphasic structure could dismiss the need for extremely accurate biomimetic mechanical properties. The use of techniques such as fiber alignment, the addition of a hydrophobic membrane (watertightness), an adhesive membrane (to avoid sutures), or the ability to prevent fibrosis as well as choosing materials with an adequate degradation rate, will contribute to the success of the substitute, more so than accurate Young's modulus or elongation at break values.

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Author Contributions

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Conflicts of interest

There are no conflicts to declare.

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Figure Legends

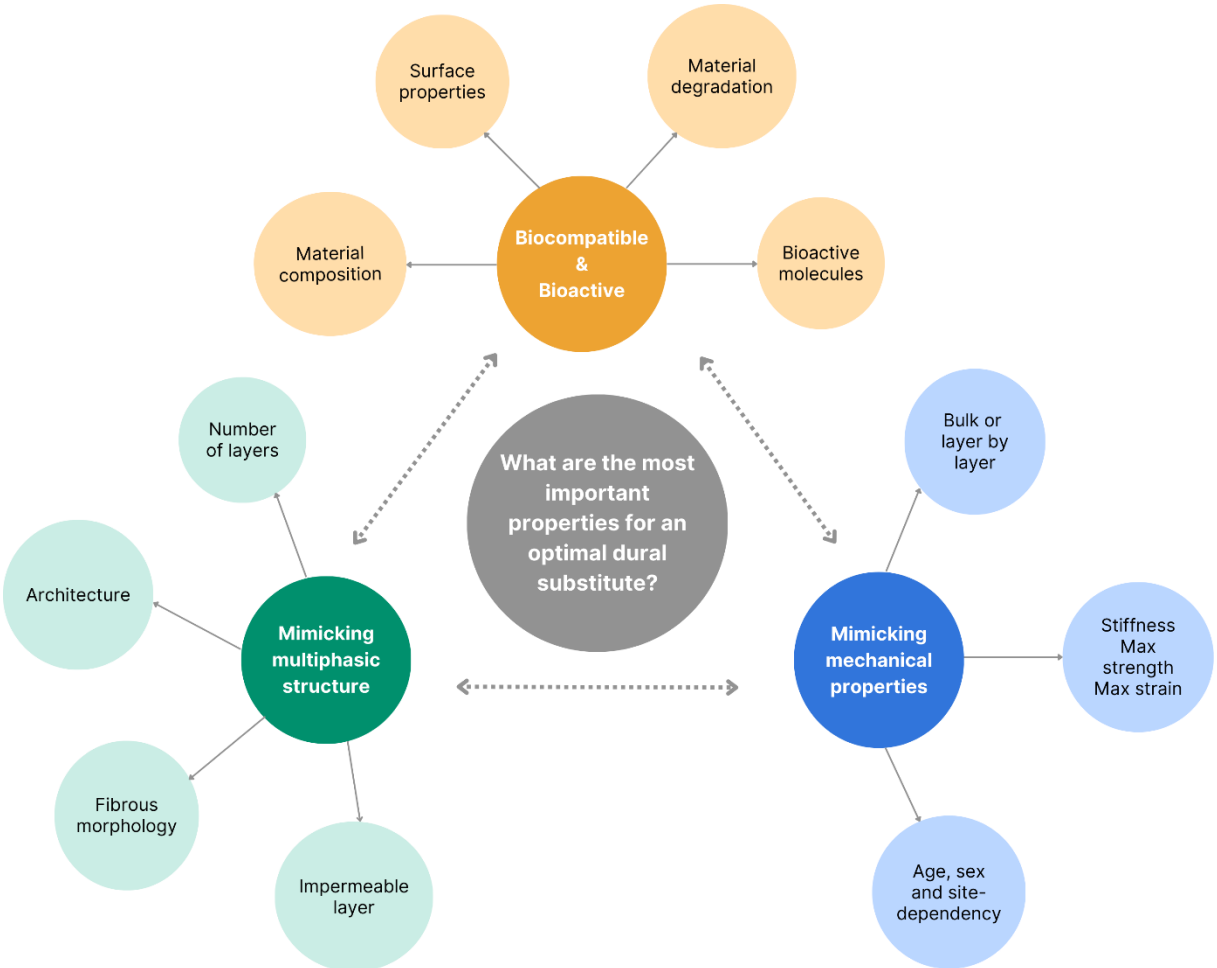

Fig. 1. Schematic illustration of the different properties (biocompatibility/bioactivity, multiphasic structure, mechanical properties) that influence the effectiveness of dura mater substitutes and may be considered to achieve an optimal substitute. Should all be included in the design of a dural substitute, or are some more important than others?

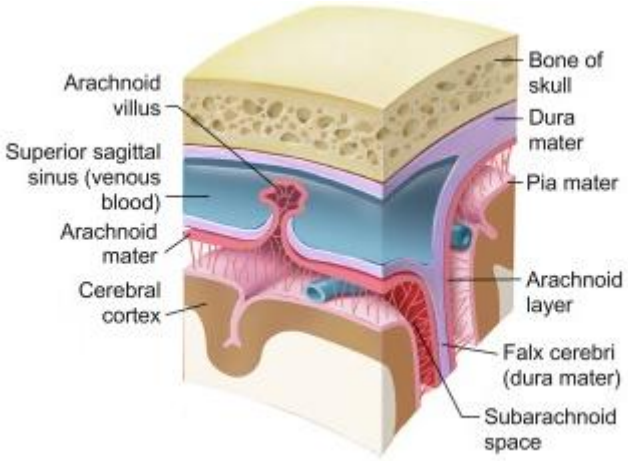

Fig. 2. Schematic representation of a cerebral section showing the meninges' three layers, the subarachnoid space and meningeal arterials and veins. The dura mater is the thickest membrane and is located close to the skull bone. Reprinted from Functional and Clinical Neuroanatomy: A Guide for Health Care Professionals, 1st edition, Moini, J., Piran, P., Chapter 4 – Meninges and ventricles, Pages 95-129.[21] Copyright 2023, Elsevier.

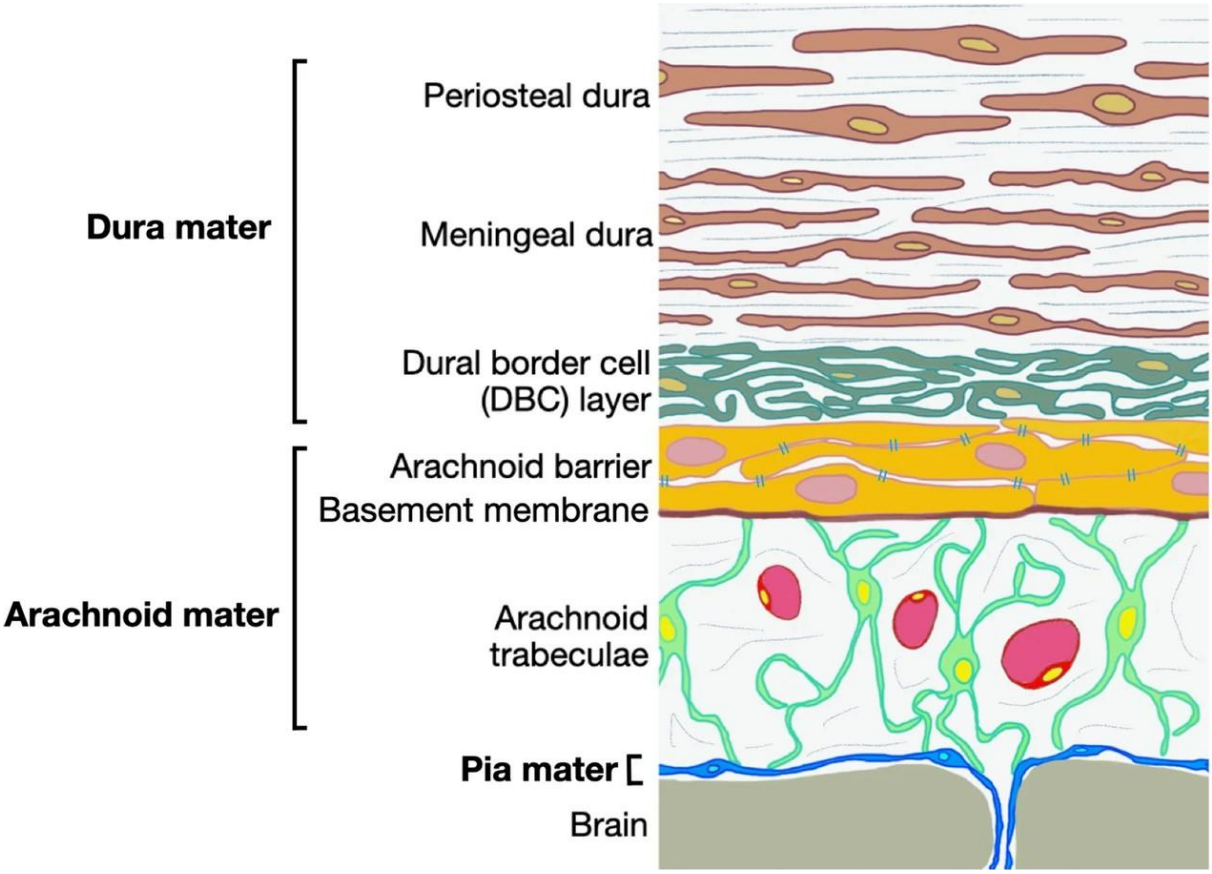

Fig. 3. Schematic representation of the structure of the dura mater. Extracellular collagen is present in the periosteal and meningeal dura layers and absent in the dural border layer. Dural fibroblasts are present in the three layers but they present a distinct phenotype in the dural border layer. Osteoblasts and elastic fibers are present in the periosteal layer. Reproduced with permission from Springer Nature.[34] Copyright 2023, Springer Nature.

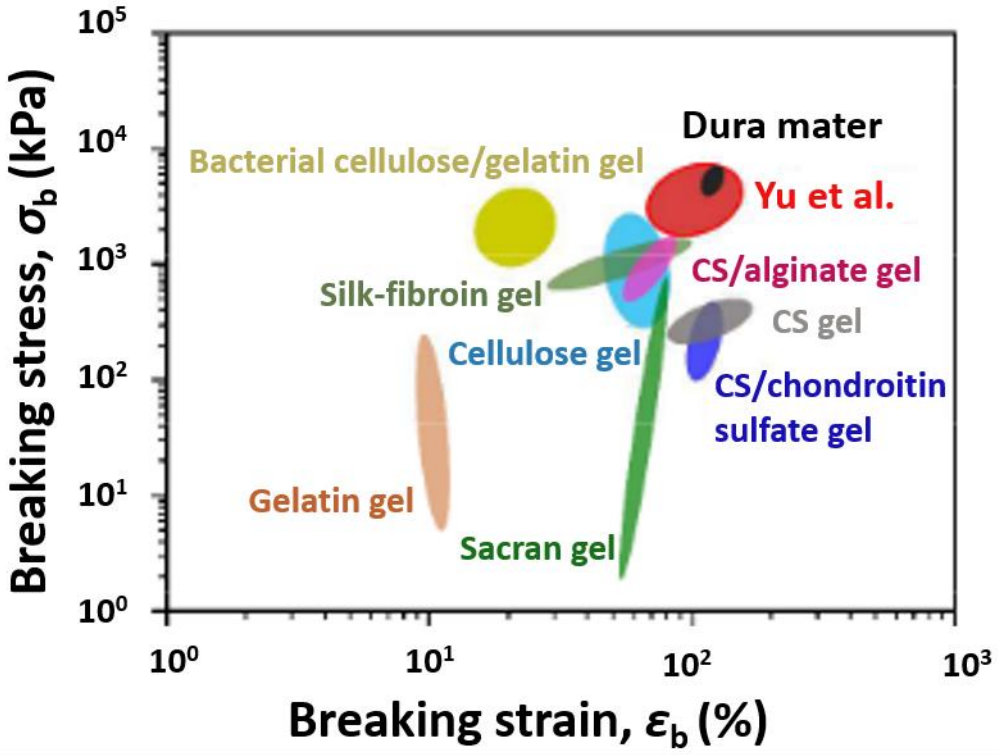

Fig. 4. Comparative chart of the strain and stress at break of native dura mater and various biopolymer-based hydrogels. A value of 116 ± 3% was reported as the reference for elongation at break of the human dura mater. Adapted with permission from Yu et al. Ultrathin κ-carrageenan/chitosan hydrogel films with high toughness and antiadhesion property. *ACS Appl. Mater. Interfaces* **2018**, *10* (10), 9002-9009.[51] Copyright 2024, American Chemical Society.

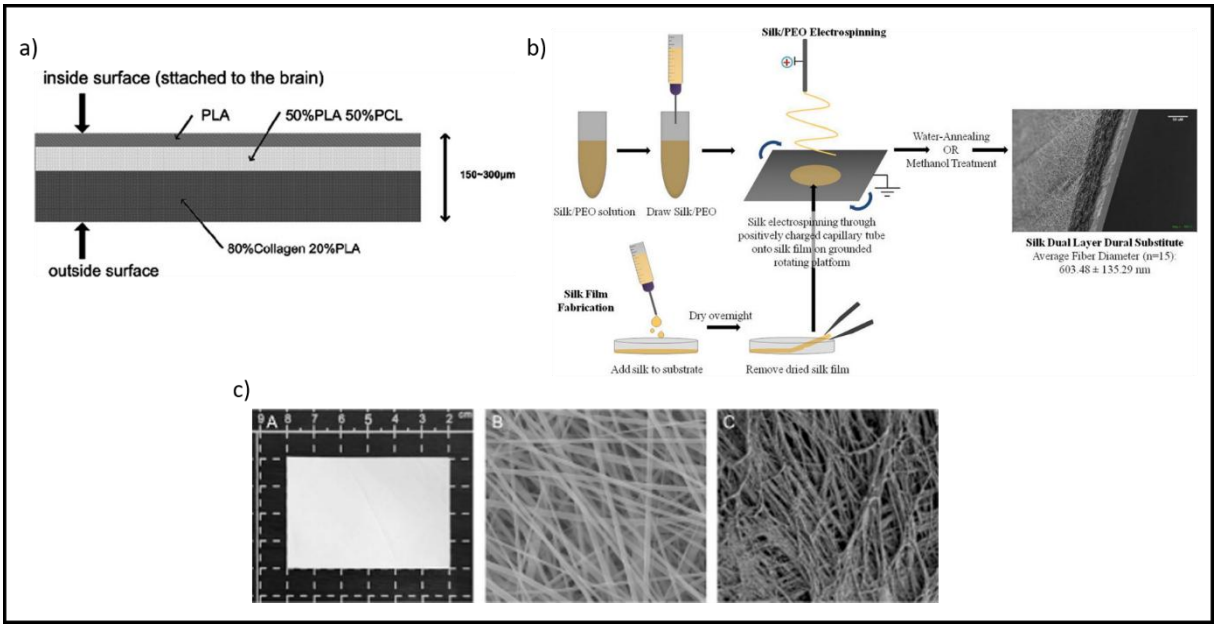

Fig. 5. Examples of multilayer dural substitutes, from triple to single layer: (a) structural diagram of a triple-layer substitute composed of PLA, PCL, and collagen produced by electrospinning. Reproduced with permission from Wang et al. Multilayer scaffold of electrospun PLA-PCL-collagen nanofibers as a dural substitute. *J Biomed. Mater. Res. B Appl. Biomater.* 2013, *101* (8), 1359-1366.[76] Copyright 2024, John Wiley and Sons; (b) schematic of a dual-layer substitute fabrication process. The solution of silk fibroin/PEO was electrospun onto an untreated silk fibroin film forming a double-layer membrane. Reproduced with permission from Flanagan et al. Development of a sutureless dural substitute from *Bombyx mori* silk fibroin. *J Biomed. Mater. Res. B Appl. Biomater.* 2015, *103* (3), 485-494.[6] Copyright 2024, John Wiley and Sons; (c) one-layer PLLA fibrous membrane: (A,B) macro and microstructure (SEM) images of the biomimetic dural substitute, (C) SEM image of the native human dura mater. Reproduced with permission from Shi et al. A new absorbable synthetic substitute with biomimetic design for dural tissue repair. *Artif. Organs* 2016, *40* (4), 403-413.[13] Copyright 2024, John Wiley and Sons.

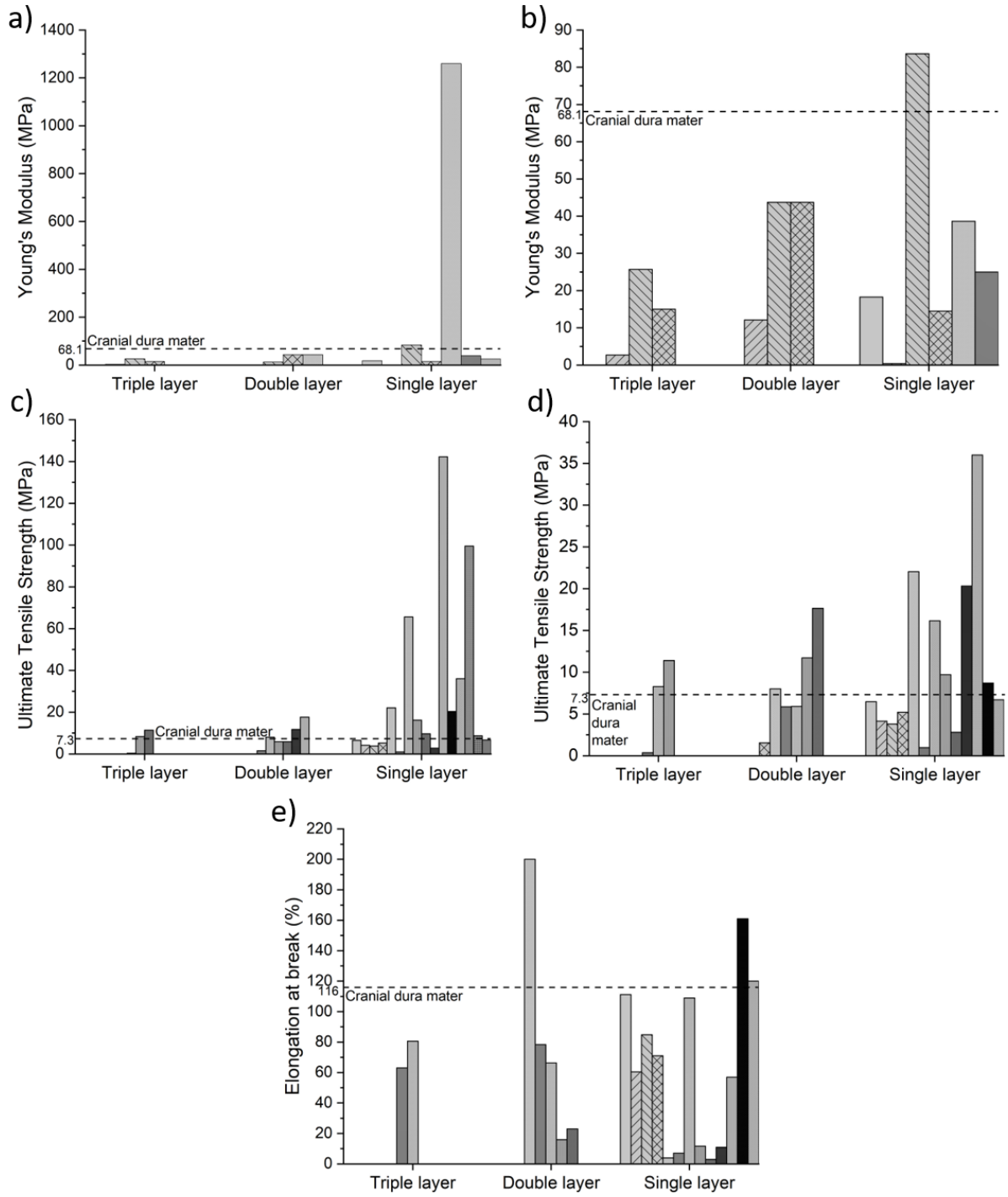

Fig. 6. The mechanical properties of multilayer dura mater substitutes and the native tissue value as comparative (dotted line). (a) The elastic modulus of each substitute and (b) the substitutes without the sample out-of-curve. (c) The tensile strength of each substitute and (d) the substitutes without the samples out-of-curve. (e) The elongation at break of each substitute.

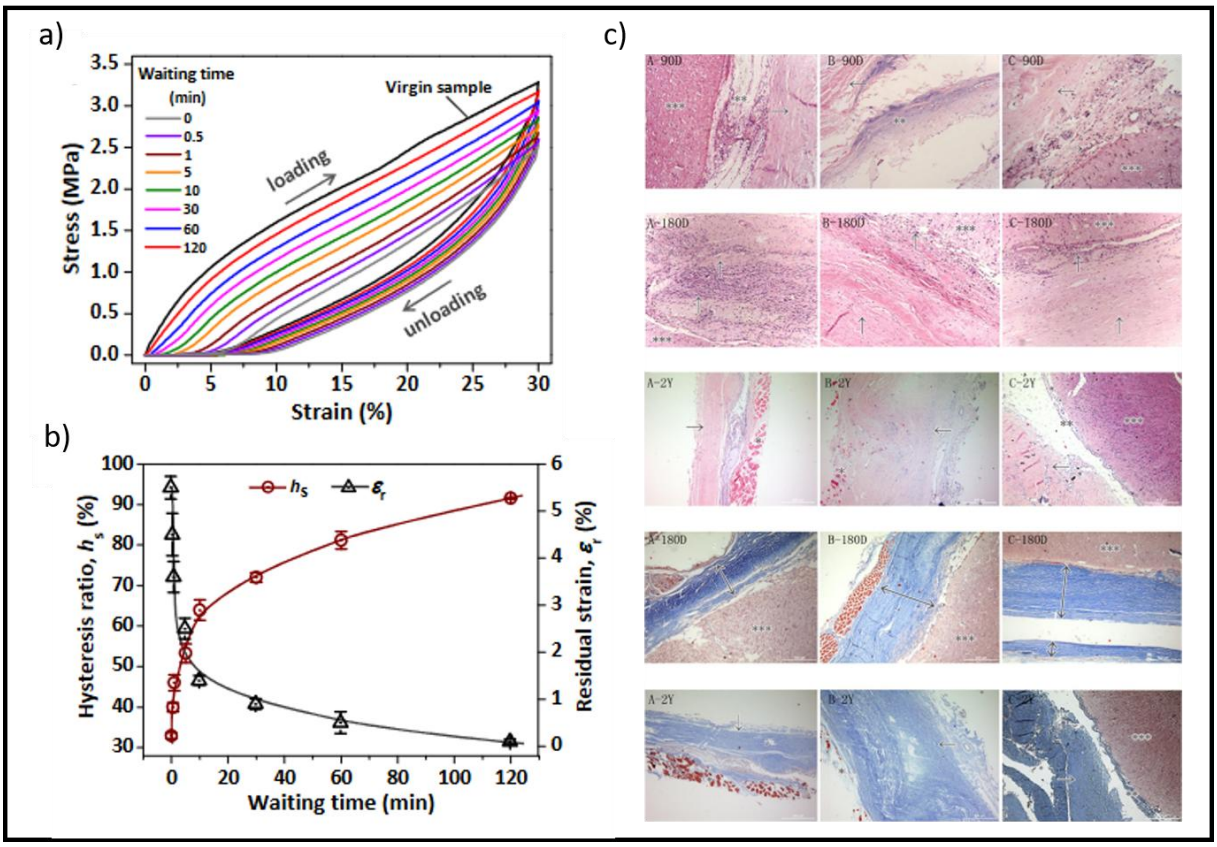

Fig. 7. Cyclic tensile (a) stress-strain curves and (b) corresponding hysteresis ratio and residual strain indicating good self-recovery property of the *κ*-CG/CS hydrogel films. Reprinted with permission from Yu et al. Ultrathin κ-carrageenan/chitosan hydrogel films with high toughness and antiadhesion property. *ACS Appl. Mater. Interfaces* **2018**, *10* (10), 9002-9009.[51] Copyright 2024, American Chemical Society; (c) Histological analysis of implanted (A) PLLA biomimetic dural, (B) NormalGEN control group, and (C) SEAMDURA control group. After 90 days, the biomimetic substitute demonstrated massive neovascularization and nearly complete degradation after 180 days, being replaced by new tissue with a reduction in the number of inflammatory cells. After two years of implantation, the three groups were found to be both safe and effective. No inflammatory cells were observed, and the substitute was completely degraded and replaced by regularly aligned fibroblasts and collagen fibers. Reproduced with permission from Shi et al. A new absorbable synthetic substitute with biomimetic design for dural tissue repair. *Artif. Organs* **2016**, *40* (4), 403-413.[13] Copyright 2024, John Wiley and Sons.

Table 1. Cranial dura mater substitutes and their processing technique, mechanical properties, and efficacity. Values equal to or less than half the native tissue value are highlighted in red; values equal to or greater than twice the native tissue value are highlighted in blue. Native tissue: E_{mod} = 68.1 MPa, UTS = 7.3 MPa and EB = 116%.

Material	Process	Biomimetic claimed	Layer	E_{mod} [MPa]	UTS [MPa]	EB [%]	CSF leakage	Other complications	Ref
PLLA/ CS/ Gelatin/ SIS	Electrospinning/ Hydrogel	**Yes**	3	2.7 ± 0.3	0.366 ± 0.002	63 ± 4	No	No	[91]
PLA/ PCL/ Collagen	Electrospinning	**Yes**	3	NS	8.28 ± 0.98[a] 8.68 ± 1.24[b]	80.66 ± 7.24[a] 80.52 ± 6.76[b]	No	No	[76]
L-lactic acid acid-ϵ-caprolactone/ PGA	Compression	No	3	27.5 ± 8.09	11.4 ± 2.84	NS	No	No	[61]
PLLA/ PGA/ PCL	Hot press molding/ Compression	No	3	15	NS	NS	No[c]	NS	[68]
Silk fibroin/ PEO	Solvent casting/ Electrospinning	**Yes**	2	7.16 ± 0.66 – 12.1 ± 2.4	0.88 ± 0.1 – 1.53 ± 0.45	NS	No[c]	NS	[6]
PLCL/ PPG/ Sodium acetate	Electrospinning	**Yes**	2	NS	> 8 – > 2[d]	> 200	No	No	[97]
ORC/PCL	Coating	**Yes**	2	15.36 ± 4.78 – 43.74 ± 6.2[e]	2.79 ± 0.14 – 5.85 ± 0.27[e]	77.48 ± 7.1 – 78.39 ± 13.24[e]	For P10 composition	No	[93]
ORC/ PCL	Solution infiltration/ Coating	**Yes**	2	15.4 ± 4.8 – 43.7 ± 6.2[e]	2.8 ± 0.1 – 5.9 ± 0.1[e]	55.4 ± 17.4 – 66.3 ± 13.1[e]	No[c]	NS	[94]
BC/ CS/ O-CMCH/ GA	Filtration/ Drying	**Yes**	2	NS	11.71 ± 1.63[a] 7.98 ± 0.57[b]	15.88 ± 0.69[a] 23.93 ± 1.38[b]	No[c]	No	[98]
BC/ CS/ O-CMCH/ CA	Filtration/ Drying	**Yes**	2	NS	17.64 ± 0.69[a] 3.20 ± 0.36[b]	23.01 ± 3.26[a] 29.24 ± 0.66[b]	No[c]	No	[98]
Poly (D-lactic acid)/ g-TTCP	Electrospinning	**Yes**	1	NS	6.46 ± 0.07	111.2 ± 4.7	NS	NS	[50]
PLLA	NS	**Yes**	1	NS	4.14 ± 0.18	60.5 ± 13.2	No	No	[13]
PLLA/ Gelatin (Neodura™)	NS	**Yes**	1	NS	3.8 ± 0.34	84.87 ± 8.45	No	No	[99]

Collagen/ PLGA	Co-electrospinning	No	1	NS	5.2	71	NS	No	[102]
PTFE (Gore-Tex®)	NS	No	1	18.26 ± 8.45	22.03 ± 0.6	NS[f]	NS	NS	[103]
Bovine skin collagen (Durepair®)	NS	No	1	54.16 ± 4.82	19.59 ± 0.65	NS[f]	NS	NS	[103]
Bovine pericardium (Tutopatch®)	NS	No	1	NS	3.51 ± 0.63	NS[f]	NS	NS	[103]
Biosynthesized cellulose	Bacteria culture	No	1	0.37 ± 0.02	0.96 ± 0.02	4	NS	No	[104]
Silk fibroin	Solvent casting	No	1	NS	65.6 ± 7.1	7.0 ± 0.6	No	No	[66]
PCL/ Gelatin	Electrospinning	No	1	NS	8.01 – 16.14[a/e] 8.65 – 22.06[b/e]	38 – 109[a/e] 32 – 125[b/e]	NS	No	[105]
Bacterial cellulose	Electrospinning	No	1	83.64 ± 22.04	9.7 ± 2.56	11.62 ± 0.6	No	No	[106]
P4HB	Electrospinning	No	1	14.5 ± 4.2	2.79 ± 0.24	NS	No	No	[107]
Bacterial cellulose/ CS/ Glycerol	Synthesis/ Freeze drying	No	1	NS	29.4 – 142.24[e]	1.97 – 2.99[e]	NS	NS	[108]
PHB/ at-PHB	Solvent casting	No	1	660 ± 60 – 1260 ± 120[e]	10.1 ± 0.9 – 20.3 ± 0.5[e]	6.4 ± 0.2 – 10.9 ± 2.6[e]	NS	No	[109]
Segmented PCL	Polymerization	No	1	NS	> 36	NS	Minimal risk	Minimal inflammation	[69]
PCL/ HAMA/ IGF-1	Blend/ Electrospinning	No	1	38.6 ± 0.13	99.53 ± 6.7	56.96 ± 4.62	NS	NS	[100]
PLGA/ TMP/ CS	Electrospinning	No	1	NS	8.71 ± 1.03	161	NS	NS	[110]
k-CG/ CS	Hydrogel	No	1	1.2 – 25[e]	2.0 – 6.7[e]	80 – 120[e]	NS	NS	[51]
HA/CMC	Hydrogel	No	1	0.12 – 0.82[g]	0.20[g]	39[g]	NS	NS	[101]

E_{mod} elastic modulus, *UTS* ultimate tensile strength, *EB* elongation at break, *NS* not stated, *PHB* polyhydroxybutyrate, at-*PHB* amorphous atactic polyhydroxybutyrate, *PLGA* poly (lactic-co-glycolic acid), *PTFE* polytetrafluoroethylene, *P4HB* poly (4-hydroxybutyrate), *ORC* oxidized regenerated cellulose, *TMP* tetramethylpyrazine, *HA* hyaluronic acid, *CMC* carboxymethyl cellulose.
[a]dry state values; [b]wet state values; [c]no *in vivo* test conducted; [d]value of the parallel and orthogonal axis to the aligned fibers; [e]range values for different compositions; [f]information provided by a graph, unspecified values; [g]compression test.