

Review

Sustainable hydrogels from slaughterhouse waste: Vitreous humor for tissue engineering applications

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ABSTRACT

Bioprocessing of slaughterhouse waste has paved the way for sustainable tissue engineering approaches that align with circular economy principles. Recent research demonstrates that efficient waste management across the entire food system can repurpose discarded tissues to extract bioactive molecules, tissue/organ templates, and biphasic materials. Hydrogels are notable examples of such materials, consisting of a unique porous network of biological macromolecules and liquid components. This architecture allows them to retain water while preserving their structural integrity and mechanical properties. The vitreous humor (VH) represents a compelling case within this paradigm. This perspective review explores the potential of animal-derived VH as a biomaterial for therapeutic applications by outlining its key structural and functional characteristics and examining its upcycling into functional hydrogels. The review then evaluates the biophysical properties of this gel obtained from both conventional (bovine, ovine, porcine, and caprine) and exotic (camelid) animal sources. Insights from the literature suggest that VH-based hydrogels show promise for various applications in additive manufacturing and regenerative medicine. Finally, the review identifies critical gaps in the research and challenges that must be addressed to facilitate the clinical translation of VH-derived biomaterials.

1. Introduction

Slaughterhouses generate approximately 150 million tons of biological waste annually, of which nearly 60 % is discarded [1]. Currently, a minor fraction of these by-products are utilized to produce agricultural products such as animal feed and fertilizers or as renewable bioenergy and biofuels [2]. Despite growing interest in sustainable valorization, the majority of slaughterhouse waste continues to be disposed of through costly and environmentally hazardous methods. These practices continue to contribute to significant ecological damage, including soil degradation, air pollution, and the spread of contaminants that pose serious risks to both human and animal health [2,3].

Nevertheless, the overlooked potential of slaughterhouse by-products, rich in collagen, keratin, nutrients, and minerals, presents

valuable opportunities across various industrial and medical sectors [2,4,5]. One particularly promising clinical application is their sustainable use in tissue engineering, where these materials can be repurposed to power implantable devices [6], generate bioactive molecules [7,8], create tissue/organ templates [9,10], and form biphasic materials like hydrogels [11]. Such advances can, in turn, support the development of pharmacological testing platforms, scaffold optimization, physiological and pathophysiological process simulators, biomechanical and biochemical analyses, cellularization, and computational modeling efforts [12–14]. This strategy not only offers a unique eco-conscious solution to existing logical challenges of abattoir waste disposal but simultaneously addresses the critical need for accessible transplantable tissue and organs. As the global demand for donor tissues continues to outpace supply, repurposing biological waste provides a viable pathway

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to help mitigate the donor shortage crisis.

Hydrogels are three-dimensional (3D), cross-linked polymer networks capable of absorbing and retaining significant amounts of water. Their structural and mechanical properties closely mimic those of the extracellular matrix (ECM), making them highly effective scaffolds for tissue engineering and cellularization [15]. Furthermore, hydrogels are well-suited for biomedical applications due to their ability to move through the body with minimal disruption and form in situ scaffolds that conform to the implantation site [16]. Features, such as a porous architecture, high biocompatibility, and tunable biodegradability, further support their use in regenerative medicine and tissue engineering [17,18]. Notably, hydrogels can serve as cell-laden bioinks, enabling the fabrication of patient-specific constructs that reduce the risk of organ rejection, enhance organ viability, and help meet the growing demand for donor organs.

Located within the posterior cavity of the eye, between the lens and the retina, the vitreous humor (VH), or vitreous body, is a transparent gel-like (ECM) [19,20]. composed predominantly of water, the VH provides structural support to the retina, facilitates metabolic solute diffusion, and allows light transmission to the posterior photoreceptors. Its inherent viscoelasticity enables it to absorb mechanical shock, offering protection against contusion-related injuries [19]. As a natural

biomaterial, the VH supports enhanced scaffold-cell interactions due to its unique composition, which includes protein-based compounds, such as collagen, as well as polysaccharides, like hyaluronic acid, heparin sulfate, and chondroitin sulfate, along with various bioactive molecules [21]. These properties position animal-derived VH as a promising naturally occurring hydrogel for use in functional scaffold development, particularly for ocular graft engineering.

Despite the VH being a naturally occurring hydrogel, few studies have explored its potential applications in tissue engineering. A search conducted on Scopus in early September 2024 using the keywords “slaughterhouse waste AND VH AND regenerative medicine” returned no results. In contrast, a broader search for “VH AND regenerative medicine” retrieved five articles, of which only four were directly relevant. These articles provided insight into: (1) the use of intravitreal injections and hydrogel-based systems as versatile platforms for drug delivery and VH replacement therapy [22]; (2) the occurrence of acute inflammation and associated immunopathological mechanisms following surgical implantation of mycoplasma-infected induced pluripotent stem cell-derived retinal pigment epithelial (iPS-RPE) cells into the eyes of healthy primates [23]; (3) the properties and clinical applications of injectable hydrogels in the treatment of ophthalmic diseases, including age-related macular degeneration, cataracts,

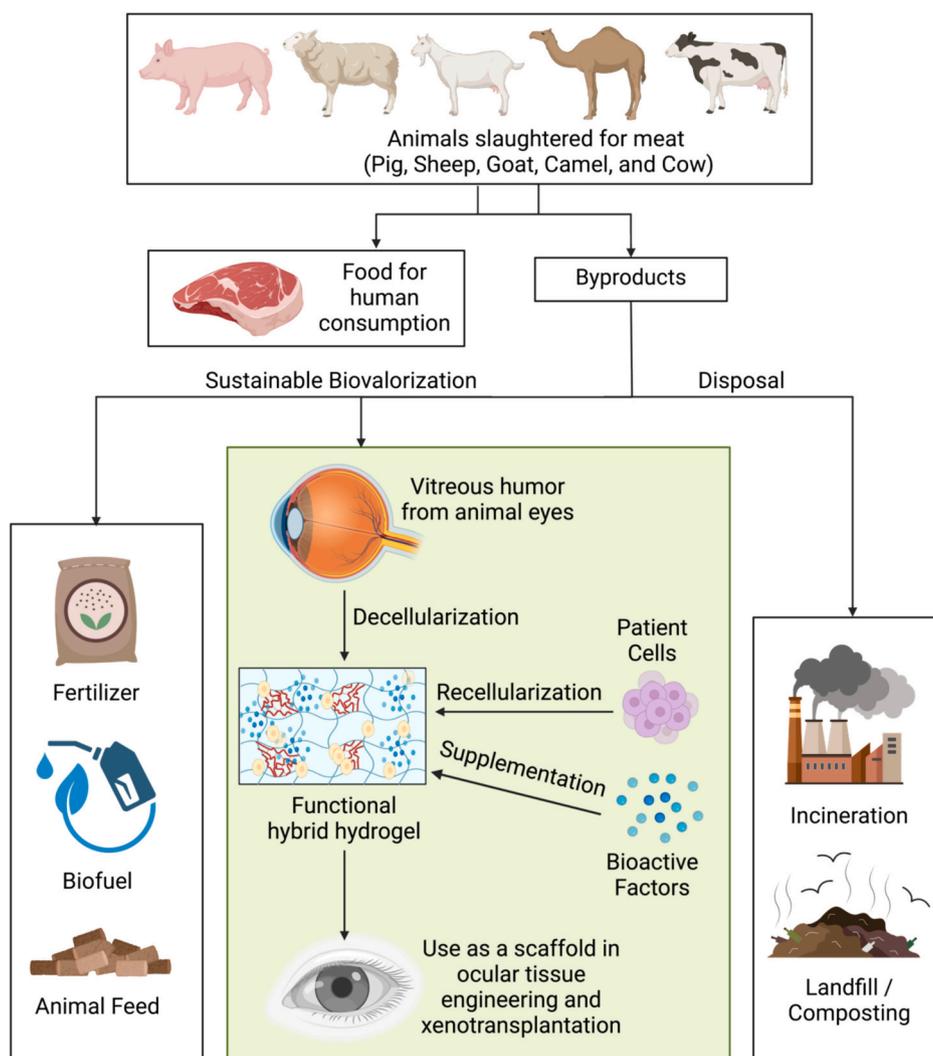


Fig. 1. An overview of the predominant disposal methods and biovalorization of animal by-products. The primary products into which slaughterhouse waste is currently recycled include fertilizers, biofuels, and animal feeds; however, due to the high cost of such repurposing, most by-products are disposed of in landfills or incinerated. The schematic outlines our proposed animal VH biovalorization method to produce functional hydrogels for ocular tissue engineering, effectively reducing the amount of slaughterhouse waste that would otherwise be disposed of by the above methods.

diabetic retinopathy, glaucoma, and intraocular cancers [24]; and (4) stem cell delivery and survival via intraocular injections into the vitreous cavity in rodent models [25]. The 5th article briefly referenced the VH in a general anatomical overview related to ocular tissue regeneration [26]. Additionally, Scopus AI, a new artificial intelligence tool designed to provide topic summaries, returned a listing of 6 references derived from 679 seminal citations. However, none of these studies directly addressed the intersection of slaughterhouse waste, VH, and regenerative medicine. Instead, these cited works primarily focused on the potential use of slaughterhouse waste in regenerative medicine more broadly [1,3,27–29], and on forensic applications of the VH in post-mortem investigations [30,31].

Remarkably, a first-of-its-kind study has demonstrated the successful use of this natural component as an ECM-based hydrogel to support chondrogenic differentiation [32]. Using freshly processed (<24 h) and cryopreserved (<3 months at $-20\text{ }^{\circ}\text{C}$) equine ocular tissues collected from slaughterhouses, establishing a viable and reproducible model. Key outcomes included minimal residual DNA content ($0.4 \pm 0.4\text{ }\mu\text{g}/\text{mg}$ dry-weight), robust proliferation of human mesenchymal stromal cells and articular chondrocytes, preservation of ECM components, and spheroid self-assembly – all in the absence of cytotoxicity and U937 macrophage-like cell activation (Fig. 1).

These promising findings, coupled with the abundance of similar biological materials, can be harnessed by the rapidly growing multi-billion-dollar hydrogel market [33], and the limited number of comprehensive reports in the field, underscore the relevance of our

current work. Here, we aim to establish a foundation for a regenerative framework grounded in the biovalorization of slaughterhouse-derived ocular tissues.

This review explores the potential of upcycling intact vitreous gels from slaughterhouse waste into natural hydrogels for regenerative medicine. Specifically, we aim to:

1. Characterize the physicochemical and biological properties that make VH a promising hydrogel for tissue engineering;
2. Compare the key properties, such as transparency, viscoelasticity, and biochemical composition, of VH from traditional (bovine, caprine, and ovine) and exotic (camelid) animal sources to those of the human VH;
3. Discuss the challenges that must be overcome to enable clinical translation of VH-derived hydrogels; and
4. Identify current knowledge gaps and research opportunities to advance the development of the VH as a functional scaffold and biomaterial.

2. Characteristics of the vitreous humor

2.1. Structure and function

The vitreous cavity is primarily divided into four main regions: the vitreous base, central vitreous (vitreal core), Cloquet's or Sterling's (hyaloid) canal, and the vitreous cortex (Fig. 2c). The vitreous base and

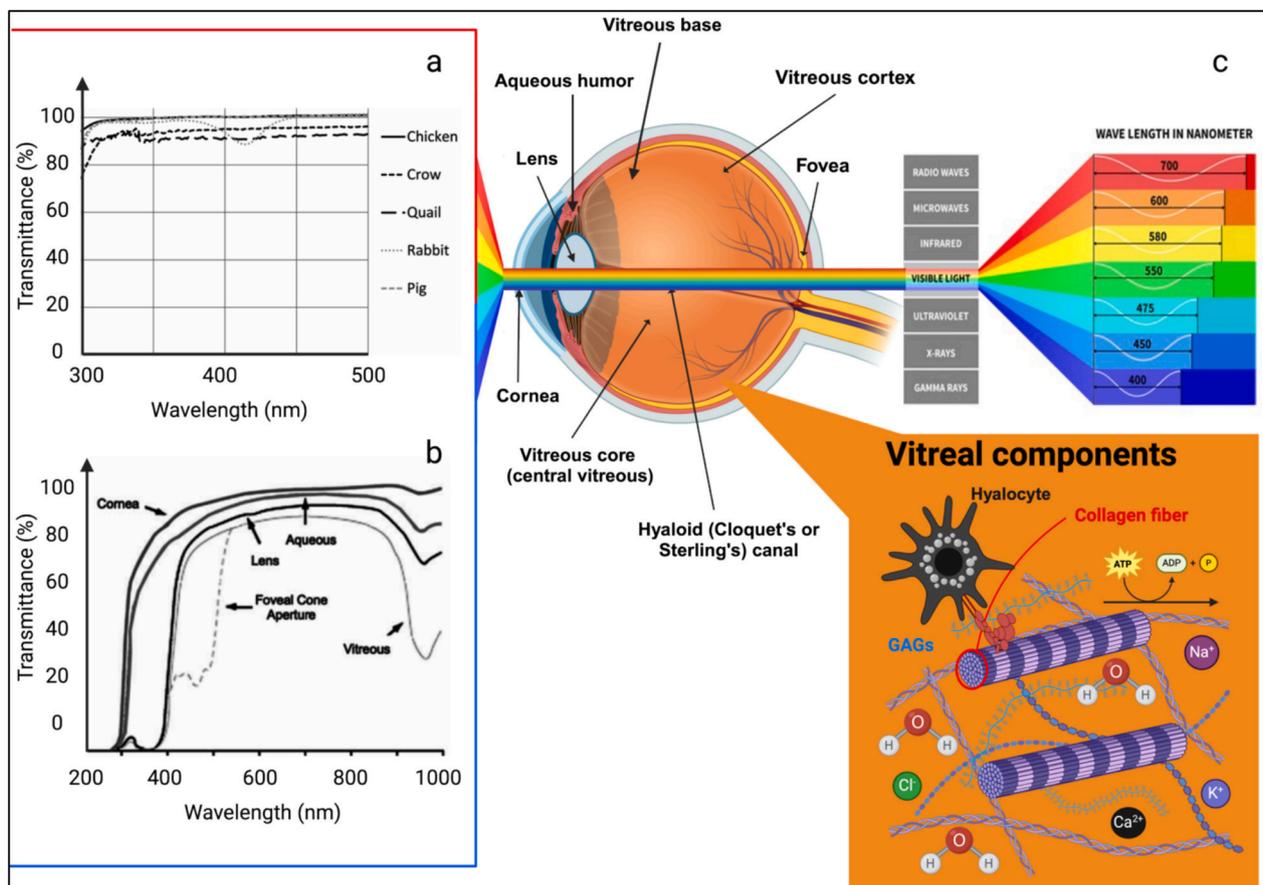


Fig. 2. A schematic of the eye highlighting the major vitreal compartments that facilitate light transmission and comparison through various ocular media, emphasizing the characteristics of the VH in multiple vertebrates. (a) Transmittance of visible light through the VH of common avians and land mammals [110]. (b) The transmittance data for corneal, lens, foveal, aqueous, and VH compartments are based on measurements from freshly enucleated human eyes [111]. (c) A depiction of light propagation throughout the eye and dispersion into various visible wavelengths. This image also illustrates the following macroscopic components: the vitreous base, central vitreous, vitreous cortex, and Cloquet's or Sterling's canal (hyaloid canal), as well as its essential microscopic components (water, hyalocytes, electrolytes, ATP, GAGs, and collagen) that characterize its potential as an ideal hydrogel.

cortex are peripheral regions that provide strong adhesion between the vitreous body, the retina, and the ciliary body. The outermost layer of the vitreous body, adjacent to the retina and the lens capsule, is thinner than the central vitreous and contains higher concentrations of collagen and hyaluronic acid.

The central vitreous occupies the bulk of the cavity and consists primarily of water, with relatively lower concentrations of collagen, hyaluronic acid, and other macromolecules that contribute to its gel-like consistency. Overall, the VH constitutes a transparent, gel-like ECM [19,20], characterized by an exceptionally high water content. It provides essential structural support to the retina, facilitates metabolic solute exchange, and allows the transmission of light to the retina. Its inherent viscoelastic properties help it absorb mechanical shocks, thereby protecting the eye against contusion-related trauma [19]. The hyaloid canal traverses the vitreous body from the optic nerve disc to the posterior lens capsule. It is a vestigial remnant of the embryonic hyaloid artery system, which once supplied nutrients to the developing lens and VH.

2.2. Physicochemical and biological properties

The VH's remarkable ocular function and structure depend on a finely tuned interplay among its optical transparency, viscoelastic behavior, and biochemical composition. Understanding this triad is essential to characterizing the VH's role in ocular physiology and its potential as a natural hydrogel. The acellular and macromolecule-sparse nature minimizes light scattering, permitting approximately 90 % transmission of visible and near-infrared light [34]. Likewise, the VH has a higher viscosity than water, enabling it to act as a mechanical damper that absorbs impacts and protects the lens and retina [35]. This mechanical resilience also contributes to the maintenance of ocular shape and the stability of delicate internal structures.

While transparency and viscosity of the VH are generally conserved across species, its biochemical composition, though based on common components, varies considerably. Such variability is not only influenced by species-specific differences but also by age-related and degenerative changes that can alter transparency, viscosity, and molecular content.

Despite limited literature and the likelihood of unaccounted species-specific patterns and consequences, it is reasonable to infer that traits associated with vitreous syneresis, which is well-documented in humans, may also occur in both common and exotic livestock. Syneresis refers to the process of vitreous gel liquefaction, which is primarily initiated by the enzymatic breakdown of type IX collagen with the ECM. Such degradation exposes the more adhesive type II collagen fibers that promote fibril fusion, ultimately leading to substantial and debilitating alterations in the native cavity [36].

Network depolymerization can also be driven by elevated activity of hyaluronidase [37] and matrix metalloproteinase 2 (MMP-2). These effects are often associated with increased levels of vitreous plasmin (ogen), which activates MMP-2 and recruits neutrophils that release proteolytic enzymes targeting collagen, fibrin [38,39]. The resulting degradation of structural fibers and the expulsion of water lead to cavity shrinkage and increased pressure on the posterior wall of the eye, generating shearing forces that erode the retinal lining. Additionally, plasmin contributes to the dissolution of adhesion molecules, such as laminin and fibronectin [40], further promoting cellular detachment. This cascade increases light scattering and compromises the structural integrity of the VH, causing irreversible damage given the gel's non-regenerative nature [41].

Collectively, the structural and functional characteristics of the VH closely align with the defining features of an ideal hydrogel [42,43]. These characteristics include its innate abundant water content, tunable rheological properties, optical clarity, cytocompatibility, and capacity to encapsulate and release bioactive compounds [44]. To further illustrate this biomedical potential, the following section will explore how these structural and functional attributes underpin the hydrogel-like nature of

the VH.

2.2.1. Transparency

Research on VH transparency across species offers valuable insights into the structural adaptations that facilitate visual acuity. Although interspecies data remain limited, existing studies reveal notable differences in light transmittance among the ocular media of birds, mammals, and other vertebrates [45]. Within mammals, pigs are frequently studied due to their physiological similarities to humans, making them a clinically relevant model.

As shown in Fig. 2(a and b), the light transmission profiles for human and porcine VH show similar trends: both exhibit low transmission rates (<20 %), in the ultraviolet range (300–400 nm range), followed by a steep increase in the visible range (400–700 nm). The porcine VH shows slightly higher transmission rates than the human VH, indicating a close match in optical properties between the two species. These findings support the translational relevance of porcine models in biomedical applications and comparative biological studies.

Although the transparency data for the camel VH remain limited, it is plausible that camels exhibit similar or perhaps higher VH clarity, potentially as an evolutionary adaptation to the arid climates and high-intensity solar radiation. Likewise, data on the VH transparency of other livestock species such as sheep, goat, and cow are still lacking. However, based on their close phylogenetic relationship and reported similarities to the porcine VH, it is reasonable to hypothesize that these species possess comparable optical properties conducive to efficient light transmission in varied ecological settings.

Transparency is a desirable property of hydrogels in tissue engineering, as it aids real-time, non-invasive evaluations of tissue formation, cell behavior, and scaffold integration using fluorescent dyes and imaging techniques. This optical property supports precise monitoring of hydrogel performance and enhances its value in optimizing tissue regeneration outcomes.

2.2.2. Cellular composition

Over the years, several studies have characterized the VH as virtually acellular, with the exception of peripheral hyalocytes [36]. However, cytological analyses have identified additional cellular elements, including nervous system-derived cells (e.g., retinal pigmented epithelial, RPE, cells and glial cells), immune cells (e.g., leukocytes and macrophages), and connective tissue components (e.g., fibrocytes, fibroblasts, and myofibroblast-like cells) [46]. Notably, the acellular nature of the VH presents a significant advantage for hydrogel generation, as it simplifies the decellularization process compared to tissues with higher cellular densities [47]. This is particularly important for applications in regenerative medicine, where minimizing the risk of immune rejection is critical. In some cases, mild centrifugation has been shown to effectively facilitate VH decellularization [32].

The primary resident cellular component of the VH is the hyalocyte, which is a specialized macrophage located predominantly in the cortical region near the vitreous base [48]. Hyalocytes contribute to the synthesis and remodeling of the vitreous matrix, particularly through the regulation of hyaluronic acid and collagen turnover. In addition to their structural role, these motile cells secrete factors that inhibit the proliferation of retinal pigment epithelial cells [49] and endothelial cells [50], respond to sites of damage, and modulate immune responses [51,52].

The overall paucity of cells within the VH is a key factor contributing to its transparency, as increased cellular content can scatter light and impair vision. This intrinsic sparsity not only supports the visual function of the eye but also represents a practical advantage in biomedical applications. Specifically, the low cellularity of the VH facilitates a more straightforward decellularization process relative to tissues with denser cellular compositions, making it well-suited for hydrogel development in regenerative medicine.

2.2.3. Viscoelastic and mechanical properties

The viscosity of the VH plays a critical role in maintaining ocular structure and function. This biophysical property contributes to the preservation of the eye's shape, supports intraocular pressure regulation, and helps maintain optical clarity [53].

Due to its intrinsic viscoelasticity, the vitreous body functions as a mechanical damper, absorbing impacts and shielding surrounding tissues from mechanical stress. This viscoelastic resilience is essential, given the constant movement of the eye during waking hours. Despite the fixations and saccades, the VH withstands significant low-frequency mechanical stress, friction, and vibration. Primarily attributed to its high hyaluronic acid content, which a gel-like consistency rather than that of a simple, viscous solution.

Consequently, the VH is an effective shock absorber, protecting sensitive ocular structures from abrupt mechanical forces [54]. However, this protective capacity diminishes gradually with age due to vitreous liquefaction. The gelatinous matrix undergoes phase separation, characterized by shrinkage of the gel component and aggregation of collagen fibrils, disrupting the normal collagen-hyaluronic acid network and forming pockets of liquid. This structural deterioration compromises the VH's biochemical integrity and reduces its capacity to buffer mechanical stress, thereby increasing the risk of retinal tearing and detachment. Furthermore, recent findings suggest a correlation between the degree of liquefaction and the onset of cataract formation, underscoring the role of vitreous biomechanics in broader ocular pathophysiology [55].

In addition to its essential cushioning function, the natural vitreous component plays a pivotal role in establishing the crucial oxygen gradient between the lens and retina. This gradient is vital for ocular health, as it ensures that a high oxygen concentration is available near the metabolically active RPE cells while maintaining a lower oxygen concentration near the oxygen-sensitive lens epithelial cells. This delicate balance is partly facilitated by the high concentration of ascorbic acid within the VH. Ascorbic acid is believed to contribute significantly to maintaining this oxygen gradient, thereby supporting the metabolic needs of the retina and preserving the health and function of ocular tissues [55]. The physical characteristics of this substance, such as viscosity, also play a crucial role in regulating this gradient via diffusion, convection, hydrostatic pressure, osmotic pressure, and active transport mechanisms [34].

Below, we explore specific measurements of VH viscoelastic properties and highlight the need for further research as we examine this property in both common and exotic livestock species (Table 2). From this data, one can identify that the VH of sheep exhibits a storage modulus (G') of 4.2 ± 0.62 Pa at 1 Hz and 6.7 ± 0.48 Pa at 0.1 Hz, indicating a strong elastic nature that is ideal for structural resilience and ocular protection (Shafaie et al., 2018). Compared to sheep, the bovine and porcine VH have substantially lower viscoelastic properties. Specifically, the storage and loss moduli of 1.7 ± 0.31 Pa at 1 Hz and 0.4 ± 0.19 Pa at 0.1 Hz for the cow and 2.5 ± 0.45 and 1.8 ± 0.35 for the pig, respectively, suggest a more fluid-like consistency that may influence the efficiency of intraocular nutrient transport, waste elimination, and potential to liquefy (Shafaie et al., 2018). Meanwhile, human VH possesses a storage modulus similar to that of cows (1.4 ± 0.95), facilitating the eye's capacity to accommodate dynamic movements without compromising its structure [56]. Unfortunately, data on camelid and caprine species are currently unavailable.

Nevertheless, given the strong agreement between the genetic maps of caprines and ovines, particularly with homologous loci mapping to equivalent chromosomes, it is possible to envision comparable viscosities among these two species [57]. In contrast, camels, which have adapted to arid and extreme environments, possess unique physiological traits that support survival in such conditions. These distinct evolutionary pressures may lead to noteworthy differences in the viscosity of their VH compared to that of other species. Given its central role of hyaluronic acid in determining vitreous viscoelasticity, its

concentrations are provided here for illustrative purposes only.

2.2.4. Biochemical composition

The complex biochemical composition of the VH plays a crucial role in ocular health, impacting a multitude of structural (e.g., cushioning) and functional (e.g., light transmission) aspects. Although this tissue is predominantly composed of water, it contains many key molecules that contribute to its structural and functional characteristics across different species. For instance, previous studies have documented as many as 1205 distinct proteins [58], which coexist with various organic acids, amino acids, carbohydrates, nucleosides, vitamins, amines, phospholipid precursors, organic acids and derivatives, and polyols [59].

The intact vitreous biochemical components comprise approximately 99 % water, 0.9 % salts, sugars, <0.1 % collagen fibrils (type II, V/XI, and IX), and glycosaminoglycans (GAGs) like hyaluronic acid [60]. VH occupies a significant volume in the eye, as this gelatinous substance spans the space between the lens and retina to help maintain structural integrity and intraocular pressure. Comprising roughly 80 % of the intraocular volume [61], a value that varies across species (Table 1), it is rich in dense collagen fibers to help regulate intraocular pressure [62]. This is demonstrated by the complete dissolution of the VH following collagenase digestion [56]. Its extremely high water content and the presence of naturally occurring polymers, specifically collagen and hyaluronic acid, make it both biocompatible and biodegradable.

Within the cortex, the most prevalent metabolite is lactate. Additionally, amino acids arginine, glycine, and methionine are combined to form the guanidino compound known as creatine, whose main function is to catalyze the conversion of ADP into ATP. Glycerol and creatine are also crucial for osmoregulation. As the primary excitatory neurotransmitter in the retina, glutamate is converted to glutamine synthetase to mitigate its neurotoxicity. Glutamate-based cortical vitreous characterization may be linked to this well-known neuronal survival strategy. Under normal physiological conditions, astrocytes and Müller glia cells remove excess glutamate and convert it to glutamine; thus, this metabolic feature is reflected in the greater representation of glutamine in the cortical vitreous. This observation emphasizes glutamine's protective role in the VH.

Comparatively, the core contains key metabolites such as glucose and acetate. Glucose is the primary substrate for ATP production. Furthermore, throughout life, vitreous glucose levels tend to mirror serum concentrations, with normal levels ranging from 0 to 180 mg/dl. Interestingly, the eye's homeostatic mechanism keeps VH glucose levels below 100 mg/dl, even when blood sugar levels reach 500 mg/dl. Acetate, an organic acid, is involved in the metabolism of acetylcholine, lipids, and carbohydrates. A thorough examination of core vitreous data reveals that the molecular profile of this less metabolically active area promotes the passive diffusion of these energetic molecules across the VH, making them available to the more metabolically active regions near the retina.

For the third compartment, the basal vitreous near the lens and trabecular meshwork contains key metabolites such as branched-chain

Table 1

Comparison of the VH volume in the cow, sheep, pig, goat, camel, and human. The various volumes of the gel are presented, and human data are included for comparison. Data on cows, pigs, goats, and humans were obtained from the following sources [108,109]. However, we could not find comparable data on the camel, so we used measurements from our experimental database.

| Species | Approximate volume of vitreous humor (ml) |
|---------|---|
| Cow | 20 |
| Sheep | 7 |
| Pig | 4 |
| Goat | 4 |
| Camel | 10 |
| Human | 4 |

Table 2

Comparison of the viscosity of the cow, sheep, pig, and human VH. Complex viscosity [η^*], storage [G'], and loss [G''] modulus measurements are shown for oscillatory stress sweep test taken at linear viscoelastic region (LVR) for VH samples from cows, sheep, pigs, and humans at 1 Hz and frequency stress sweep test at 0.1 Hz. The hardness (N) of the samples was measured using a texture profile analyzer, which was adapted from [56]. Human and hyaluronic acid (HA) data are included for comparison.

| Species | G' [Pa] (1 Hz) | G' [Pa] (0.1 Hz) | G'' [Pa] (1 Hz) | G'' [Pa] (0.1 Hz) | $[\eta^*]$ (1 Hz) | $[\eta^*]$ (0.1 Hz) | Hardness (N) |
|---------|---------------------------|--------------------------|-------------------------|------------------------------|-------------------------|---------------------------|-----------------|
| Cow | 1.7 ± 0.31 | 0.4 ± 0.19 | 0.7 ± 0.12 | 0.5 ± 0.25 | 0.3 ± 0.05 | 0.9 ± 0.51 | 10.9 ± 0.36 |
| Sheep | 4.2 ± 0.62 | 6.7 ± 0.48 | 2.3 ± 0.56 | 3.7 ± 0.45 | 0.9 ± 0.24 | 1.23 ± 0.94 | 21.2 ± 0.71 |
| Pig | 2.5 ± 0.45 | 2.5 ± 0.45 | 2.5 ± 0.45 | 2.5 ± 0.45 | 2.5 ± 0.45 | 2.5 ± 0.45 | 2.5 ± 0.45 |
| Human | 1.4 ± 0.95 | – | 0.7 ± 0.37 | – | 0.3 ± 0.25 | – | – |
| HA | 0.7 ± 0.12 | 0.05 ± 0.02 | 1.7 ± 0.04 | 0.3 ± 0.03 | 0.3 ± 0.01 | 0.5 ± 0.05 | 12.2 ± 3.41 |

Table 3

Summary of advancements in the field.

| Materials | Animal source | Key findings | References |
|---------------------------------|-------------------------|--|--|
| Vitreous humor | Equine | <ul style="list-style-type: none"> Low cytotoxicity VH can be used with multiple cell lines Aid in chondrogenic differentiation | Lindberg, 2019 https://doi.org/10.1016/j.actbio.2018.12.022 |
| Vitreous humor and silk fibroin | Bovine | <ul style="list-style-type: none"> Silk fibroin addition improved physicochemical properties Increase in corneal epithelial cells adhesion and proliferation | Sepideh Rafiei, 2024 https://doi.org/10.1002/bip.23612 |
| Vitreous humor | Arabian sheep and camel | <ul style="list-style-type: none"> Novel method to extract polyunsaturated fatty acids from eyes Fatty acid composition was similar in both species. However, linoleic acid was absent in sheep eyes | Mayssa Hachem, 2024 https://doi.org/10.1016/j.heliyon.2024.e38148 |

amino acids (BCAA), betaine, alanine, ascorbate, lysine, and myo-inositol [63]. Ascorbate regulates oxygen levels in the eye, ensuring adequate oxygenation for the vascularized retina while protecting sensitive tissues such as the lens and trabecular meshwork from oxidative stress. Its differential concentration, with a higher representation near the cortical vitreous, suggests resistance to reactive oxygen species (ROS) diffusion from active retinal areas. This distribution is most likely due to the differential expression of vitamin C transporters, particularly sodium-ascorbate cotransporter 2 (SVCT2), which is more abundant in the distal retina.

Osmoregulatory molecules like betaine and myo-inositol also contribute to the basal vitreous metabolic signature. Betaine regulates cell volume and influences enzymes like phosphorylase kinase and glycogen metabolism. Myo-inositol, essential for many cellular processes, maintains the osmotic balance required for retinal structure and function. Elevated levels of myo-inositol and betaine in the basal vitreous may indicate local activity aimed at preserving the neuroretina environment, regulated by selective transporter density in anterior segment cells. The presence of branched-chain amino acids (BCAA) in

the basal zone suggests an alternative energy source to glucose, predominantly found in the cortical area. BCAA's role in energy metabolism, particularly in the citrate cycle and ATP production, highlights its significance in maintaining retinal tissue function.

While data on the human vitreous is well-documented, Supplementary Table 1 illustrates that the composition of this gel across various displays distinct biochemical profiles relevant to ocular function. Firstly, collagen concentrations vary substantially, with the bovine VH containing 684 $\mu\text{g/ml}$ compared to 149–384 $\mu\text{g/ml}$ in the ovine VH, reflecting species-specific differences in structural support. Secondly, hyaluronic acid levels range from 50 to 570 $\mu\text{g/ml}$ in cows to 100–1070 $\mu\text{g/ml}$ in sheep, indicating its variable role in maintaining the vitreous gel consistency and viscoelasticity. Thirdly, ascorbic acid concentrations are nearly identical in cows (170 $\mu\text{g/ml}$) and sheep (165 $\mu\text{g/ml}$), underscoring a conserved antioxidant function. Fourthly, hexosamine and hexuronic acid levels are relatively comparable, with cows having 350 $\mu\text{g/ml}$ of each, while sheep present 190 $\mu\text{g/ml}$ and 177 $\mu\text{g/ml}$, respectively. Fifthly, nitrogen content is lower in cows (157 $\mu\text{g/ml}$) than in sheep (212 $\mu\text{g/ml}$), and sialic acid levels are higher in sheep (440 $\mu\text{g/ml}$) than in cows (350 $\mu\text{g/ml}$), potentially reflecting differences in cellular communication or surface glycosylation. Lastly, hydroxyproline, which is indicative of collagen turnover, is reported only in sheep (20 $\mu\text{g/ml}$), suggesting species-specific differences in collagen subtype or metabolic activity.

Overall, these differences underscore the specialized adaptations of each species to their environments and physiological demands, with implications for disease susceptibility and functionality. While several metabolites, including amines (choline, dimethylamine, and trimethylamine oxide), phospholipid derivatives (glycerophosphocholine and phosphocholine), organic acids and their derivatives (betaine, creatine, scyllo-inositol, and tyrosine), and polyols (glycerol) have been identified, the available data remain insufficient for meaningful cross-species comparison. This scarcity of published information further emphasizes the need for further research to clarify the roles of these components within species-specific physiological and pathological contexts.

3. Biovalorization of vitreous humor: extraction and potential upscaling methods

A conceptual framework to support the biovalorization process for upcycling vitreous humor (VH) from traditional and exotic animal sources relies on proper extraction, sterilization, and purification techniques, as shown in Fig. 3. Adequate short- and long-term storage protocols are essential to maintain hydrogel properties and enable bioprocessing and characterization, including decellularization and recellularization steps.

The recovery of vitreous humor from ocular globes requires meticulous handling to ensure integrity and sterility. The method to harvest and store ocular components from slaughterhouse waste is described by Lindberg et al. [32,64]. Typically, whole eyes are sourced from abattoirs or processing plants, where they are prepared for fresh or stored collection. After harvesting by cutting the ocular nerve (Fig. 3a), submersion in sterile phosphate-buffered saline (PBS) enriched with antibiotics (penicillin and streptomycin) minimizes microbial contamination during cooled transportation (Fig. 3b). Maintaining a cold chain from collection to the research facility is crucial for reducing degradation. Fresh eyes can be used immediately, while long-term storage involves freezing at $-20\text{ }^\circ\text{C}$ or $-80\text{ }^\circ\text{C}$, with the latter being preferred for its superior preservation capabilities.

Pre-extraction decontamination involves removing excess connective tissue and the anterior segment of the eye using aseptic techniques. This step often includes washing with ethanol to ensure eye surface decontamination (Fig. 3c). Extraction methods vary; one involves making a large incision and carefully removing the VH with forceps, while another uses a syringe to aspirate the VH through a small incision (Murali et al., 2015). Both methods aim to minimize disruption and

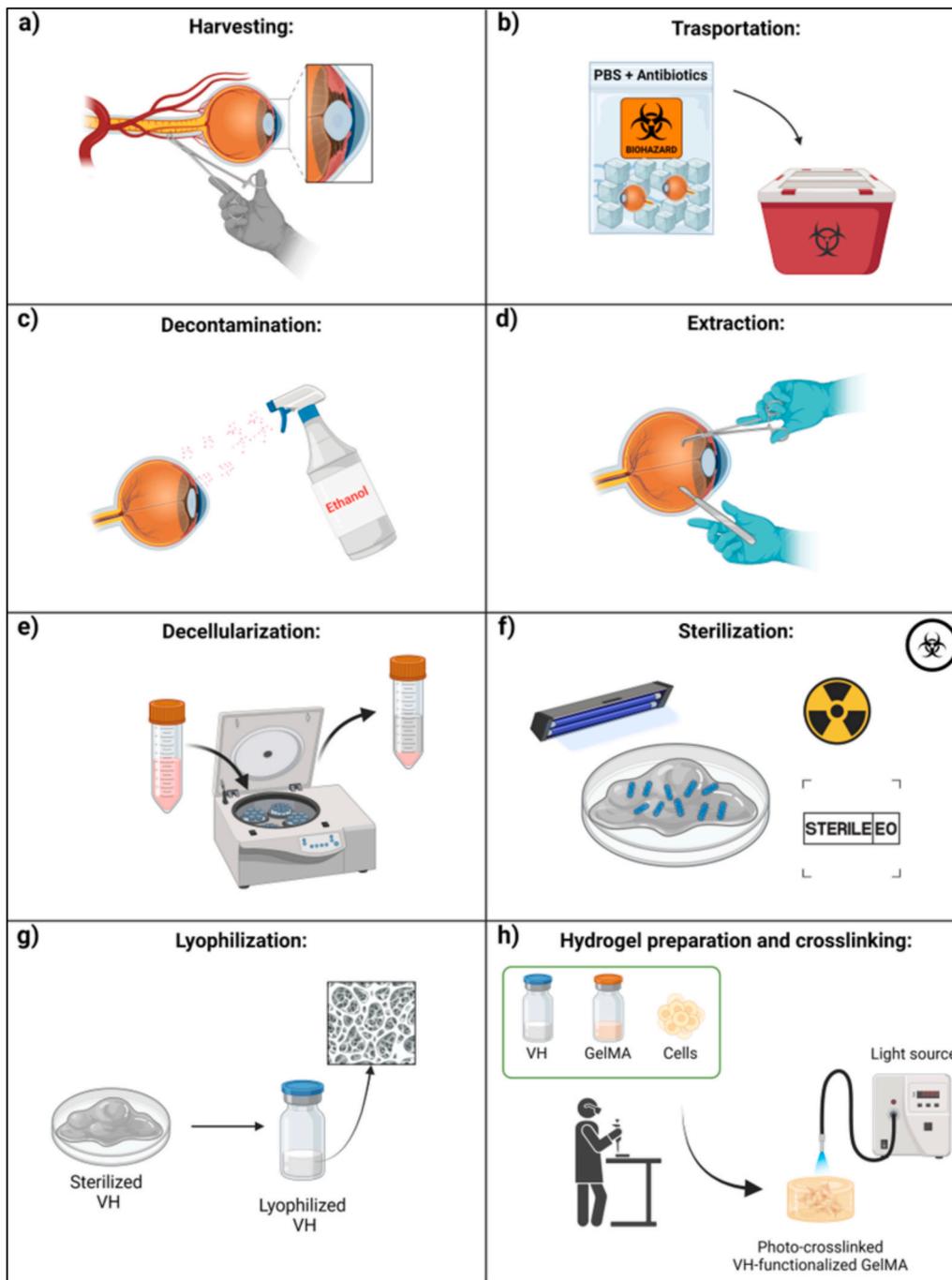


Fig. 3. A proposed biovalorization model that rapidly generates cost-effective hydrogels. This model outlines the valorization of slaughterhouse biowaste in 8 steps, from the waste collection to the application stages, including a) organ harvesting; b) immersion in saline containing antibiotics and transportation in ice; c) decontamination by using ethanol externally; d) extraction of the VH using tweezers in combination with a scalpel or scissors; e) decellularization via ultracentrifugation; f) sterilization of VH using UV light (or more clinically relevant methods like gamma rays or treatment with ethylene oxide) followed by sterility tests to ideal discover bacterial growth; g) lyophilization of the sterilized VH by using a freeze-dryer; and h) hydrogel preparation by mixing GelMA hydrogel and lyophilized VH under a biological hood, followed by its photo-crosslinking (by using a light source), which can be further functionalized for cellular and biomolecular seeding.

maintain VH integrity (Fig. 3d).

After extraction, the VH is processed to remove cellular debris through centrifugation (Fig. 3e). The decellularized VH is sterilized via UV light exposure. Given UV light's limited penetration, inverting the gel and repeating UV exposure can enhance sterility. Alternatively, gamma irradiation or ethylene oxide treatment can be applied for in vivo application standards (Fig. 3f). In some cases, sterilizing the entire globe before extraction may be advantageous to avoid post-extraction

degradation. Regardless of the method, the hydrogel should be handled in sterile conditions throughout the process, and sterility should be confirmed via microbial assays before cell culture applications. Testing hydrogel compatibility with the target cell types is essential to ensure functionality.

Storage conditions also influence gel integrity. Short-term at $-20\text{ }^{\circ}\text{C}$ is convenient but can lead to ice crystal formation that damages the collagen-hyaluronic network. Though it is cost-effective, it increases the

contamination risk. In contrast, -80°C storage better preserves complex biochemical structures by slowing down enzymatic and chemical activities. While it requires specialized equipment, it significantly enhances the stability of enzymes, nucleic acids, and proteins.

To minimize degradation, freeze-thaw cycles should be reduced, cryoprotectants such as DMSO or glycerol should be addressed, especially at -80°C . Storing intact, sterilized eyes may offer additional protection. VH can be lyophilized for long-term preservation (Fig. 3g), and rehydrated or blended with other biomaterials.

One potential tissue engineering approach could involve utilizing VH as a functionalization agent for another gel with favorable rheological properties, such as gelatin methacrylate (GelMA), for bioprinting or injectable formulations. In this approach, the VH acts as a functionalizing agent, complementing collagen and hyaluronic acid to promote ECM formation after cell differentiation. The final components can then be photo-crosslinked with UV or visible light to stabilize the 3D structure and improve its mechanical strength (Fig. 3h).

In conclusion, the biovalorization of VH into hydrogels offers significant economic and biomedical benefits. Their low production cost, scalability, and compositional versatility make them suitable for a range of tissue engineering applications. Ensuring proper extraction, storage, and sterilization protocols will be essential to preserving hydrogel integrity and ensuring safe, effective use in regenerative medicine and other bioprocesses. As further research continues to explore novel applications, VH-based hydrogels hold substantial promise for advancing sustainable biotechnological innovations.

4. Applications and considerations for vitreous humor as a hydrogel material in tissue engineering

Current biowaste levels from slaughterhouses and processing plants are considerable and are projected to increase in response to global demand for meat products. Unfortunately, population growth, climate change, ecological disasters, and political conflict, as well as the looming threat of global warfare and future pandemics, have intensified concerns over food insecurity [65]. In response, efforts are being made to enhance conventional practices by improving efficiency and sustainability to transform biowaste into viable products. Such approaches aim to boost food production through better-integrated supply chains committed to circular bioeconomic practices and promote biowaste valorization.

Astonishingly, only around 30 % of post-slaughter meat processing products are utilized for human consumption [66]. In contrast, the majority are discarded, with stricter regulatory oversight, limited disposal options, and public health concerns contributing to rising recycling and disposal costs [1]. Recent studies have demonstrated how upscaling slaughterhouse biowaste offers a significant potential for sustainable tissue engineering and nutrient recovery, including the extraction of fatty acids [67], enzymes [68], and hydrogels for cultured meat and tissue/organ regeneration [69–73]. Among the overlooked sources of such waste is the eye, which is an organ often discarded in large volumes. Remarkably, this underutilized tissue could support green technologies, particularly in tissue engineering applications ranging from non-invasive to invasive interventions.

Though physically small, the eye is a structurally complex and delicate organ comprising anterior and posterior compartments essential for sensory processing. It is vulnerable to cardiovascular and metabolic disorders, as well as trauma, which makes it a disease. Globally, over 285 million people suffer from visual impairments, many of which current treatments cannot effectively prevent or reverse [74]. Nevertheless, advances in ocular tissue engineering are offering promising avenues for intervention. Emerging technologies, such as artificial and bioartificial keratoprosthetics, intraocular lenses, vitreal substitutes, or drug delivery systems, could benefit from repurposing intact VH.

For instance, corneal injuries resulting from abrasions and keratitis can lead to corneal opacity and, ultimately, blindness. While minor injuries heal through peripheral epithelial cellular migration, severe

injuries often require external treatments, including topical antibiotics or steroids, synthetic drugs, phototherapeutic keratectomy, or corneal transplantation. Age-related conditions, like cataracts, macular degeneration, and syneresis, also affect the lens, retina, and VH, contributing to vision loss. Elevated intraocular pressure, as seen in glaucoma, presents another challenge. These conditions highlight the need for innovative solutions like functionalized hydrogels for wound healing [75–77], targeted drug delivery, and vitrectomy procedures. VH-derived hydrogels also hold promise for keratoplasty via cell-laden bioinks, enabling the development of next-generation ocular therapies from repurposed biowaste.

4.1. Ocular tissue engineering applications

From an additive manufacturing perspective, innovative approaches for devising functional hydrogels from the VH to manufacture intraocular and contact lenses and corneal scaffolds offer improved biocompatibility and performance over traditional materials. These hydrogels also present opportunities to develop novel ocular diagnostics. The virtually limitless supply of humoral extracts from agri-food waste can be utilized for therapeutic cell encapsulation, support for proliferation and differentiation [78], strategies to better emulate and enhance the human VH by adjusting its mechanical and biochemical properties [79], and for controlled drug delivery applications, enabling delivering site-specific therapeutic release over time while minimizing adverse side effects [80,81].

Several compounds have been studied for their potential to fill the vitreous cavity and replicate its functions. The ideal vitreous substitute should mimic all the favorable properties of the native vitreous body, such as transparency, elasticity, buffer capacity, and biocompatibility with neighboring tissues, while avoiding detrimental characteristics like liquefaction and age-related biodegradation. The creation of this ideal substance remains an unmet goal. Biochemical composition and biomechanical qualities differ significantly between species, so understanding these interspecies differences is crucial.

Accordingly, animal VH-based gels, such as cadaveric and cross-species surrogates, can be used in in situ gel reconstitution models. Vitreous augmentation or supplementation aims to restore the gel-like state of the eye's VH, which liquefies due to age-related vitreous syneresis. This process involves introducing a biocompatible, gel-like substance, potentially a synthetic or semi-synthetic hydrogel, to mimic the native VH and counteract liquefaction, floaters, or remnants from retinal detachment. Despite the theoretical benefits, challenges include ensuring biocompatibility, accurately replicating the native tissue's complex composition, and overcoming technical hurdles in delivery and integration. Interestingly, the cellularity of the VH is beneficial in immunological complications and may facilitate cross-species applications. At the same time, it is imperative to consider the potential for prion transmissibility and strategies to mitigate the associated risks of xenotransplantation [82].

The VH contains collagens and GAGs that provide structural support and maintain the hydration and elasticity of the ECM. Specifically, collagen type II, predominantly in the VH [83], forms a loose network supporting the eye's shape. Meanwhile, collagen types I, IV, V, VI, and VIII in the cornea contribute to its transparency and mechanical strength, with type I being the most abundant in the corneal stroma [4]. Additionally, both tissues contain hyaluronic acid and chondroitin sulfate, GAGs crucial for maintaining their structural integrity and function. In contrast, while the lens and VH have high collagen contents, the lens primarily comprises collagen types IV, I, V, and VI [84]. Thus, utilizing the vitreous body to generate replacement intraocular lenses or as an injectable hydrogel to reconstitute ailing and extracted lenses [24] is an intriguing prospect, given the potential refractive index matching while presenting several scientific and technical challenges related to structural stability, integration, and long-term performance.

Given the growing demand for transplantable corneal grafts and the

forementioned compositional similarities, it is reasonable to consider that VH-based bioinks could improve 3D bioprinting of corneal tissues. The biocompatible and gel-like nature of the VH makes it an excellent component to enhance bioink performance. Integrating vitreous-derived hydrogels into decellularized corneal scaffolds can better mimic the natural ECM, promoting cell adhesion, proliferation, and differentiation. Likewise, developing contact lenses capable of releasing topical medications represents another promising direction [85]. This approach would not only help address the corneal graft shortage but also expand contact lens functionality.

Developing transparent hydrogels replicating the optical characteristics of natural VH is crucial for preserving visual clarity and minimizing ocular light distortion. Leveraging the abundant reservoirs of intact hydrogels in slaughterhouse biowaste can help improve the hyaluronic acid content and collagen fiber configuration, which are key to constructing corneal scaffolds, intraocular lenses, and vitreous substitutes. Advanced manufacturing techniques like 3D bioprinting and electrospinning can fine-tune these hydrogels' microstructure, ensuring they closely mimic the natural properties of the required VH, cornea, and lens. These efforts can aid the critical need to develop future distinct yet related ocular diagnostic and therapeutic technologies. Moreover, maintaining optical clarity in the printed structures is vital to avoid visual distortions and ensure the success of ocular implants supporting in vitro and in vivo applications. By addressing these design and functional requirements, additive manufacturing can be effectively harnessed to advance novel ocular biomedical technologies.

4.2. Modified/functionalized VH for other tissue engineering applications

The VH may be reinforced with nanomaterials and naturally occurring biopolymers such as alginate, cellulose, and chitosan. Following reinforcement, the resulting VH-based composite gel can be used in many tissue engineering applications, including wound healing, as well as bone, cartilage, and cardiac muscle regeneration.

Further modifications of the VH could expand its applicability in developing customized bioinks and hydrogels for scaffold fabrication. For instance, when reinforced with conductive polymers and nanomaterials, the VH may be applied in neuronal tissue engineering. Similarly, mechanical reinforcement strategies can support the development of scaffolds to treat osteochondral defects.

Among modern fabrication techniques, 3D bioprinting and electrospinning are advanced technologies that are especially critical for biomedical applications. Specifically, 3D bioprinting enables precise, layer-by-layer construction of complex biological structures, allowing researchers to design tissue architectures tailored to specific requirements by varying key parameters such as printing speed and pressure [86]. This adaptability facilitates the development of customized constructs to accommodate different tissue types and patient-specific needs.

In comparison, electrospinning generates micro- and nano-fibrous scaffolds from polymer melts by applying a high-voltage electric field. It offers versatility in tuning fiber diameter, composition, and mechanical performance [87]. Electrospun fibers possess distinctive characteristics, including a high surface-to-volume ratio, porous structure, mechanical strength, flexibility, and resemblance to the native ECM, making them especially suitable for drug delivery and tissue engineering applications [88,89].

These methods are suitable for fabricating scaffolds with tailored pore sizes and fiber alignments, both of which are essential for efficient cell infiltration, nutrient diffusion, and tissue integration. Each technology is highly customizable and capable of producing scaffolds with specific functional properties, rendering them integral to additive manufacturing for biomedical research.

For 3D bioprinting to succeed in tissue engineering, bioinks must exhibit favorable rheological properties, such as shear-thinning viscosity, to enable precise deposition and structural fidelity. These materials

should also support high cell viability and proliferation, ensuring long-term integration with host tissues. High-resolution bioprinting is essential for replicating the intricate microarchitecture of native tissues, and studies have shown that achieving such resolution significantly enhances the functionality and biocompatibility of ocular implants [90,91].

Moreover, functional bioinks containing therapeutic agents can be used to create drug-eluting implants and wound dressings, which can provide localized, sustained drug release to aid tissue regeneration [92]. These platforms also allow for high-throughput studies and real-time physiological monitoring, with hydrogel-based sensors capable of detecting disease-related biomarkers [93]. By immobilizing sensing elements within hydrogel matrices, researchers can develop highly sensitive biosensors for wearable medical devices and clinical diagnostics [94].

Finally, cross-linking strategies are crucial in tuning the physico-chemical and mechanical properties of VH-based hydrogels. Techniques such as click chemistry may be used to functionalize the VH, broadening its utility in a range of tissue engineering applications while maintaining biocompatibility and responsiveness to environmental stimuli.

4.3. Regulatory and environmental considerations for slaughterhouse waste utilization

4.3.1. Legal approaches for slaughterhouses waste management

The development of tissue engineering applications from slaughterhouse-derived materials, such as the VH, requires alignment with established biosafety and waste-handling regulations. For instance, within the United States, the Environmental Protection Agency (EPA) has implemented specific legislation aimed at minimizing the transmission of pathogens during the treatment and disposal of slaughterhouse waste [95]. Such frameworks can serve as templates for regulatory strategies in other regions. Effective enforcement typically requires inter-agency collaboration and improved hygienic practices in abattoir operations [96].

Institutions like the World Organization for Animal Health (WOAH) play a key role in promoting global harmonization by providing guidance on safe animal handling and waste processing protocols [97]. This approach incorporates recommendations for hygienic slaughtering procedures and proper postmortem handling of by-products [98]. Regulatory systems must differentiate between types of waste, i.e., biological and chemical, and solid, and establish clear lines of responsibility and legal accountability [99]. A robust legal foundation is essential to facilitate the safe and ethical upcycling of biowaste such as VH for biomedical applications.

4.3.2. Waste management aspects for the control of slaughterhouse effluents

The proper management of slaughterhouse effluents is critical for limiting environmental pollution and ensuring biosafety during the recovery of high-value biological materials. Treatment must be tailored to waste composition, defining organic load and microbial content. Anaerobic digestion, for example, is a widely used technique that reduces waste volume and simultaneously generates biogas, thereby contributing to circular economy goals [1,97,100].

Alternative strategies such as sedimentation and microbial bioremediation with microbial agents effectively reduce nutrient runoff, particularly nitrogen and phosphorus, thus reducing eutrophication and aquatic ecosystem degradation [101,102]. Additionally, implementing pasteurization or thermal disinfection is vital for inactivating pathogens in tissues intended for medical use. These preventative measures can significantly reduce the transmission of zoonotic diseases like salmonellosis and leptospirosis, which are often associated with improperly treated slaughterhouse by-products [103].

4.3.3. Circular economy practices for upscaling slaughterhouse waste

Converting slaughterhouse waste into high-value products such as hydrogels requires integrating advanced technologies within a circular economy framework. Biowaste-to-energy systems and enzymatic valorization pathways offer dual advantages, reducing environmental pollution while generating renewable products [104]. Specific applications like tissue decellularization for scaffold engineering and biochar synthesis for agricultural use illustrate the versatility of these approaches.

Beyond technological advances, developing a skilled workforce trained in biosafety, sanitation, and regulatory compliance is essential. Educational programs that emphasize hygiene and waste management can foster a safety-first culture and support ethical biomaterial recovery [96,105]. Ultimately, successful biovalorization efforts hinge on the alignment of policy, training, and infrastructure. These elements are essential for transforming abattoir by-products into functional, safe, and sustainable biomedical resources.

4.4. Bridging experimental and translational research

In order to realize the clinical potential of VH-based, future research must address regulatory, ethical, and technical barriers. Key requirements include the development of validated decellularization and sterilization techniques, assessment of long-term biocompatibility, and compliance with biosafety and waste management regulations. Although the VH offers structural and functional similarities to native ECM, standardization in processing and quality control is necessary for broader clinical adoption.

Critical research gaps remain in crosslinking strategies, immunogenicity profiling, and degradation kinetics. Addressing these gaps will be pivotal in the transition from laboratory-based experimentation to clinical realization. Likewise, interdisciplinary collaborations, spanning materials science, biomedical engineering, regulatory science, and clinical medicine, are needed to drive translation. The incorporation of VH-derived hydrogel into injectable systems or customizable bioinks for soft and hard tissue applications presents a novel pathway in regenerative medicine. Overall, with sufficient validation and stakeholder alignment, the VH represents a suitable and scalable alternative for future biomedical innovation.

5. Substantial literature gaps and challenges

Despite the promising potential of the VH in biomedical applications, significant gaps remain in the existing literature. This is highlighted by the limited number of research articles that currently summarize advancements in the field (Table 3) [32,106,107]. While the structural and functional properties of human VH are well-documented, the paucity of comparative studies involving the VH from different animal sources represents a major limitation. A deeper understanding of the interspecific variability in biochemical composition, viscosity, and optical properties is needed, as these factors directly influence the suitability of the VH for tissue engineering and regenerative medicine applications. Furthermore, most studies focus on general properties and potential uses without addressing specific methodologies or long-term outcomes. This lack of fundamental research hinders the development of standardized protocols and limits the scalability of vitreous-derived hydrogels for clinical use.

Insights gained from studies of the human VH can help guide the sustainable utilization of animal-derived vitreous materials, particularly for restoring structural integrity and functionality in patients with degenerative ocular conditions. Addressing these knowledge gaps will allow researchers to advance the field of tissue engineering and develop innovative therapeutic strategies.

Future research can help bridge these gaps. Interdisciplinary approaches that integrate materials science, biology, and clinical medicine expertise can generate in-depth insight into VH-based technologies.

Long-term in vivo and clinical studies will also be crucial for evaluating the biocompatibility and efficacy of vitreal-derived hydrogels. In parallel, collaborations with industry partners will be vital to enable scaling up production, refining quality control processes, and translating laboratory innovations into commercial solutions.

The dual challenges of slaughterhouse waste biowaste management and the complex requirements of tissue engineering create opportunities for innovation. Overseeing the difficulties associated with maintaining the structural and functional integrity of the VH during extraction, sterilization, and storage will be key. Careful handling during recovery, adoption of advanced extraction techniques, and optimized sterilization protocols can mitigate degradation and contamination. Developing improved cryopreservation strategies that minimize freeze-thaw cycles and prevent ice crystal formation will enhance VH utility across applications.

Finally, tissue-specific customization of VH-based hydrogels via material science innovations remains a major challenge. Nevertheless, advances in this area could facilitate the formation of gels with precise biomechanical, biochemical, and optical properties suited for diverse therapeutic needs.

6. Conclusions

In summary, this review underscores the potential of the VH as a valuable biomaterial for tissue engineering applications. Historically overlooked as slaughterhouse waste, its structural and biochemical properties make it a promising candidate for functional hydrogel development. Hydrogels, exemplified by the VH's unique porous solid polymer networks and liquid components, have applications across diverse industries, including cosmetics, water purification, additive manufacturing, and regenerative medicine.

By exploring the variability in gel transparency, viscoelasticity, and biochemical composition across traditional (bovine, ovine, porcine, and caprine) and exotic (camelid) meat sources, this review highlights strategies to address current limitations and unlock opportunities for tissue engineering. This approach contributes to a more sustainable and resource-efficient future.

The increasing demand for sustainable biomaterials presents an opportunity to develop VH-derived hydrogels for various applications, such as wound healing, drug delivery, and tissue regeneration. However, further research is needed to assess the immunogenicity and degradation profiles of VH-based hydrogel to ensure safe clinical translation.

From our perspective, the future of VH-based hydrogels lies in the integration of advanced biotechnological strategies, including cross-linking methods and the incorporation of cells and nanomaterials to enhance functionality. Finally, the rapid growth of the multi-billion-dollar hydrogel market further supports the potential of developing sustainable alternatives derived from agri-food waste.

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CRediT authorship contribution statement

Peter R. Corridon: Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization. **Makayla J. Fahmy:** Writing – review & editing, Writing – original draft. **Marie Arjemandi:** Writing – original draft. **Hamda Alkaabi:** Writing – original draft. **Sara Khaled Alameri:** Writing – original draft. **Shiv Dutt Purohit:** Writing – review & editing, Writing – original draft. **Diego Trucco:** Writing – review & editing, Writing – original draft. **Leonardo Ricotti:** Writing – review & editing, Writing – original draft, Funding acquisition.

Declaration of Generative AI and AI-assisted technologies in the writing process

While preparing this work, the author(s) used Grammarly and ChatGPT to review grammar and spelling. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the publication's content.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interest: Peter R Corridon reports financial support was provided by Khalifa University College of Medicine And Health Sciences. Leonardo Ricotti reports financial support was provided by Sant'Anna School of Advanced Studies BioRobotics Institute. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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