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CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
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REVIEW

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Protein by-products: Composition, extraction, and biomedical applications

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ABSTRACT

Significant upsurge in animal by-products such as skin, bones, wool, hides, feathers, and fats has become a global challenge and, if not properly disposed of, can spread contamination and viral diseases. Animal by-products are rich in proteins, which can be used as nutritional, pharmacologically functional ingredients, and biomedical materials. Therefore, recycling these abundant and renewable by-products and extracting high value-added components from them is a sustainable approach to reclaim animal by-products while addressing scarce landfill resources. This article appraises the most recent studies conducted in the last five years on animal-derived proteins' separation and biomedical application. The effort encompasses an introduction about the composition, an overview of the extraction and purification methods, and the broad range of biomedical applications of these ensuing proteins.

KEYWORDS

Animal by-products; biomedical applications; extraction; proteins

Introduction

Every year, the world's growing population produces considerable food waste (Baiano 2014; Abduh 2016; De Schouwer et al. 2019), with discarded foods in North America and Europe alone accounting for three times the required food to feed the hungry people around the world (Stuart 2009).

Food waste can occur in the supply chain, food processing, restaurants, supermarkets, and households during production and processing. Generally, one-third of produced foods (1.3 billion tons per year) is wasted by humans during consumption (Haberl et al. 2011). According to the European Commission, about 39% and 42% of the European annual waste is produced during food processing and households, respectively (Figure 1a) (Nuutinen et al. 2019; EC-Europa and European Commission 2020). Yearly per capita waste food from the household of some countries around the world in 2020 is shown in Figure 1b (Statista 2022). Nevertheless, the scale of the food waste that is produced in Europe is more in the consumption stage. It is estimated that around 1.89 million tons of waste are generated annually in the European food industries (Table 1) (Zhu, Gavahian, et al. 2020).

In light of the food industry products, according to International Food Container Organization (IFCO) report, α 45% of fruits and vegetables, 35% of all fish and seafood, 30% of all cereals, 20% of all dairy products, and 20% of all meat and poultry products are wasted (Figure 1c). Table 1 also includes an estimate of the mass of waste generated by European food industries, with the fruit and vegetable industry producing the most waste.

Food waste generation means wasting of all-natural sources such as water, land, and energy which are used for food production. The food processing industry, consumed 117 petajoules of energy in 2017 and is the fourth largest industrial energy user that is linked to producing large-scale greenhouse gas and pollution (Ladha-Sabur et al. 2019). This is an economic burden with environmental consequences, such as pollution, climate change, the burden on scarce landfill, and an imbalance in standard environmental bioconcentrations (Mekonnen, Mussone, and Bressler 2016; Nayak and Bhushan 2019; Prandi et al. 2019). Therefore, it

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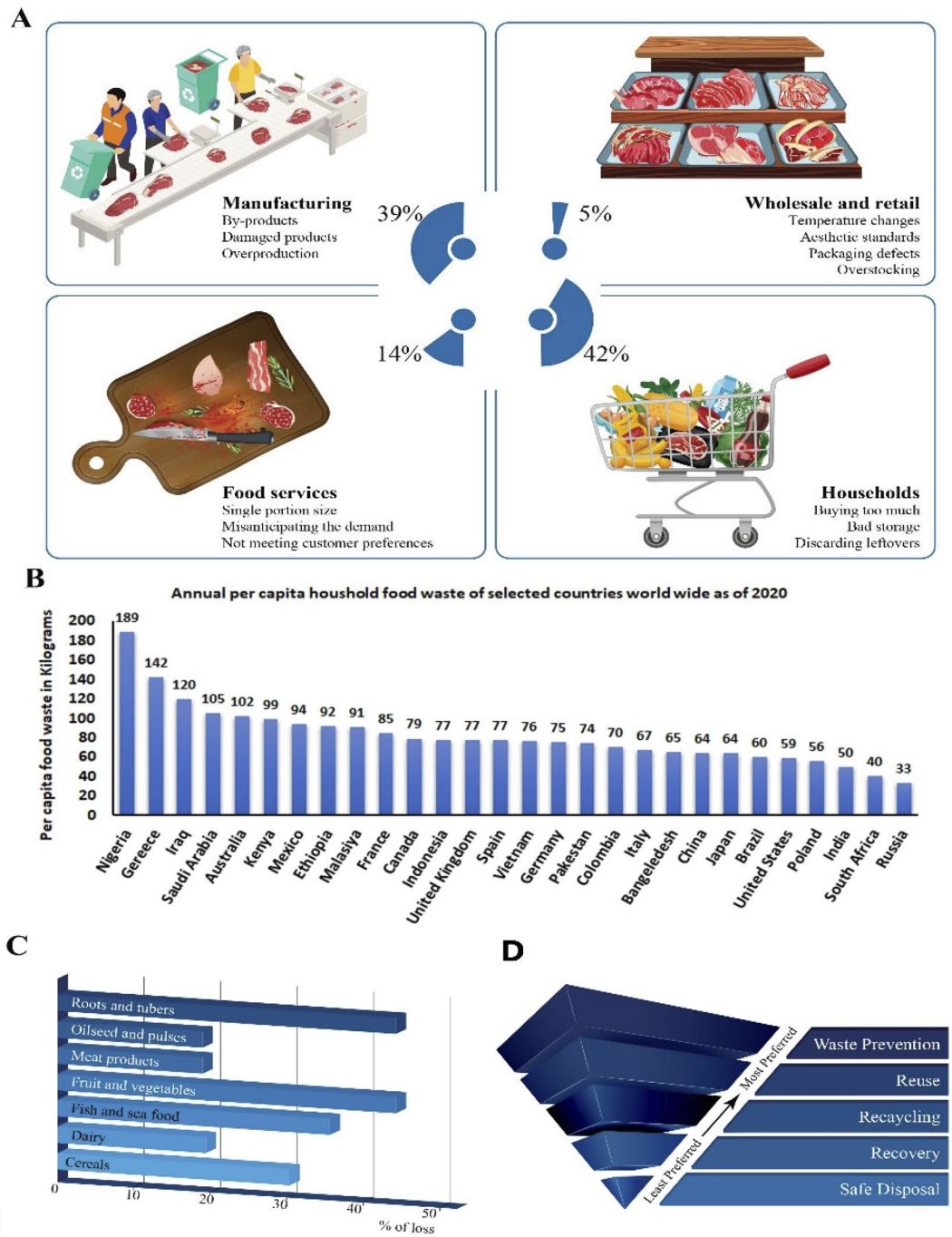

Figure 1. A) The percentage of the food waste during manufacturing, wholesale and retail, food services, and households in Europe (Nuutinen et al. 2019; EC-Europa and European Commission 2020), B) Annual per capita waste food from household of some countries around of the world at 2020 (Statista 2020), C) The percentage of food waste for various categories of food products according to food and agriculture organization (FAO) (Zhu, Gavahian, et al. 2020), and D) Accepted waste management hierarchy approaches (most preferred to least preferred) (PECB).

is essential to manage food waste and loss. Hence, in 2017, the department of the environment and energy of national food waste introduced a strategy to reduce, recycle and recover food waste. Figure 1d shows their hierarchy classification which is ranked from the most preferred to the least preferred approach, which is avoiding, reusing, recycling, reprocessing, recovering energy, and finally disposing of. The European Commission and its member for 2030 aim to halve food waste per capita (European Commission 2020).

By developing technology, there are many approaches and methods such as using chemical and biological sensors, smart packaging, and algorithms for monitoring the state of foods are in progress to reduce food waste (Aschan 2020). Several digital platforms and mobile applications like Pepperplate, Food.com, UBO, ECO dal frigo, PucciFrigo, Instock, Twiga Foods, Cheetah, and Plantix have been developed to track food consumption.

Extraction of high value-added components such as proteins, polysaccharides, fibers, aromatic compounds, and

phytochemicals from food waste is a primary technique to use the extracted components as nutritional and pharmacologically functional ingredients (Ng et al. 2020; Abduh 2016; De Schouwer et al. 2019). The type of biomolecule, the production scale (laboratory or industrial), the desired purity, and the economic value of the extracted compounds all play a role in selecting an appropriate extraction technique (Ng et al. 2020; Mekonnen, Mussone, and Bressler 2016; De Schouwer et al. 2019). To extract proteins from food-by-products, a variety of procedures have been developed, including enzymatic methods (Gaurav Kumar et al. 2017), high pressure and high temperature (Fowler et al. 2012), and acid or alkaline-based (Hukmi and Sarbon 2018) approaches. Collagen, gelatin, keratin, silk fibroin, sericin, and elastin are the primary proteins found in bio-waste (Biswal, Kumar BadJena, and Pradhan 2020; Liu et al. 2019; Rajabi et al. 2020; Feroz et al. 2020; Cascone and Lamberti 2020). These proteins are nontoxic, biodegradable, processable and easy to modify in terms of physiochemical structure and therefore have widely used in biomedical engineering (Biswal, Kumar BadJena, and Pradhan 2020; Liu et al. 2019; Rajabi et al. 2020; Feroz et al. 2020; Cascone and Lamberti 2020). Several studies (Diogo et al. 2018; Manikandan et al. 2018; Wang, Sun, et al. 2019; Ang et al. 2020; C. Ding et al. 2020; Ghorbani et al. 2020) have indicated that incorporating protein polymers into tissue engineering scaffolds improves cell adhesion and proliferation. Drug delivery methods with controllable biodegradability and enzyme immobilization capabilities in the form of micro/nano-scale particles, fibers, films, and 3D printed scaffolds have also made extensive use of protein-based biomaterials (Silva et al. 2014; Costa, Silva, and Boccaccini 2018a; Zhang, Lu, et al. 2021; Han et al. 2022; Agnieray et al. 2021).

Cao et al. currently reviewed the preparation, extraction, and application of animal by-products collagen (Cao et al. 2021). A comprehensive review of silk sericin and its application for tissue engineering has been published by Maria C. Arango (Arango et al. 2021). However, there is a lack of a comprehensive review article on protein from animal by-products to help readers to realize the differences between these proteins' composition, properties, extraction, isolation methods, purification process, and their potential as a biomaterial for biomaterials engineering. Herein, we discuss the composition of common proteins, including collagen, gelatin, keratin, silk fibroin, and elastin; review the protein extraction and purification methods; and critically summarize these proteins' applications for biomaterials engineering.

Protein by-products derived from animals

The demand for meat and meat products has increased globally over the last 20 years (González et al. 2020). In 2020, more than 400 million metric tons of fish, poultry, pig, beef and veal, and Atlantic salmon were consumed globally (Statista 2022). Figure 2a shows the daily per capita protein supply in 2017 in different countries; most countries supply more than 80 g of protein per day, indicating that animal is a major source of protein (FAO 2017). It is anticipated that a 30% rise in the current world population will result in a 70% increase in food demand by 2050. According to FAO and IFCO classifications, waste from animal by-products (fish and seafood, as well as meat and poultry products) accounts for 50 to 55% of total food waste at all stages(González et al. 2020).

Farm animals, dairy products, fishing, and the textile industry are just a few of the industries that generate waste from animal products (Abascal and Regan 2018). Farm animal waste, such as carcasses, hides and skin, feathers, wool, hooves and horns, offal, eggshell, bones, fats, meat trimmings, blood, and other fluids; waste from fishing, other than by-catches, shells, bones, skins, fins, viscera, oils, and blood are examples of industrial processing waste of animal origin (Uranga et al. 2020; Flachowsky, Meyer, and Südekum 2017; Alao et al. 2017). Non-conforming wool and silk fibers are among the textile industry's waste (Abascal and Regan 2018). We, therefore, require novel and green technologies and methods for repurposing animals' waste.

The use of animal by-products is determined by their classification. Animal by-products are classified based on structure, shape, muscularity, and color, and the classification varies by country (Fayemi et al. 2018). Non-carcass meat that is safe for human consumption (as determined by a licensed public health inspector) and non-meat (non-consumable) by-products are two categories. The animal liver, tongue, heart, and kidney are non-carcass meat, while bones, skin, hide, horns, hair, feather, hove, and bristle are placed into the non-meat group (Fayemi et al. 2018). These by-products are high in proteins, amino acids,

Table 1. Estimates of the mass of waste generated in the European food industries (Zhu, Gavahian, et al. 2020).

Industrial sector	Amount of waste (*1000 tons)	Waste (%)
Production, processing, and preserving of meat and meat products	150	2.5
Production, processing, and preserving of fish and fish products	8	3.5
Production, processing, and preserving of fruits and vegetables	279	4.5
Manufacture of vegetable and animal oils and fats	73	1.5
Dairy products and the ice cream industry	404	3
Production of grain and starch products	245	1.5
Manufacture of other food products	239	2
Drinks industry	492	2
Total	**1890**	

important nutrients such vitamins B1, B2, B6, minerals, and unsaturated fat, and can be used for human and animal food, as well as fertilizer, cosmetics, pharmaceuticals, and biomedical engineering (Figure 2b). It has been reported that over 2 billion people worldwide, specifically in developing countries, suffer from deficiency of vitamins and minerals, including iron and zinc. Approximately 20 g/day of protein from meat, fish, egg, and milk is necessary to meet these people's dietary needs. As a result, edible proteins sources can be used to compensate for insufficient protein intake (Cao et al. 2021). The inedible animals' by-products cannot be used by humans, so are rejected as waste, or reproduced into the secondary components. Table 2 summarizes the inedible animal by-product's and current primary uses and applications. For example, cattle manure, pig waste, poultry litter, and solid waste generated from meat processing are used in the biogas industry as fuel in the cyclonic combustor and electric power production (Alao et al. 2017). The hides and skins removed from a slaughtered animal are used in the cosmetic and fabric industry to produce shoes, belts, bags, gelatin, and keratin (Alao et al. 2017; Falowo et al. 2018). Moreover, some research has shown that chemical and biochemical extracts from animal by-products can be used to treat a variety of medical diseases. However, some issues related to the use of inedible proteins should be considered, such as the accumulation of heavy metals in the dried rumen or the disease that can be transmitted from animal to human such as bovine spongiform encephalopathy infection (Alao et al. 2017).

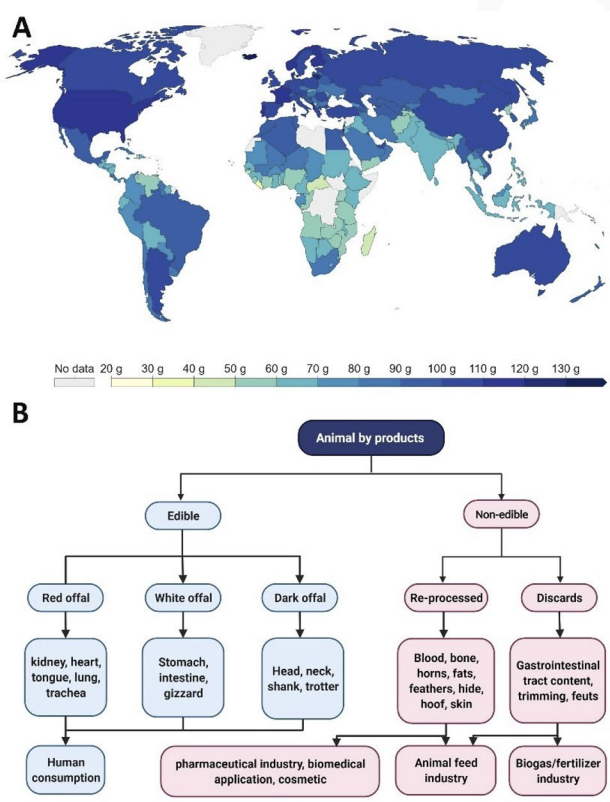

Figure 2. A) The daily per capita protein supply at 2017 for each country (FAO 2020), B) Some of the applications for animal by-products.

Structure, composition, and sources of common animal by-products proteins

The properties of the proteins such as elastin and silk are intrinsically linked to their composition, typically multiple tandem repeats of short amino acid sequences. Depending on how these amino acids are connected, a protein will be endowed with certain qualities (Biswal, Kumar BadJena, and Pradhan 2020; De Schouwer et al. 2019; Lo and Fauzi 2021). Figure 3 shows animal sources and primary structures of some common proteins.

Collagen

Collagen is the most abundant protein in the Extra cellular Matrix (ECM) of the human body that comprises 25-35% of the total body content (Lim et al. 2019), which is known as a viscoelastic material with high tensile strength. At least 29 types of collagens have been identified to date, varying in function, distribution, and range in tissues (Lim et al. 2019). Over 90% of the available collagen in the human body is the type I, while other common collagens are types II, III, and IV (Abascal and Regan 2018; Lim et al. 2019; Ocak 2018; Yavuz et al. 2020). Table 3 presents the most common collagen types in mammalian tissues.

Collagen is a trimeric molecule whose fundamental structure with three polypeptide α chains, two amino acid α_1 chains, and one amino acid α_2 chain (Figure 4a(left)) with a diameter of 10 to 500 nm, a molecular weight of 285 kDa, and a length of 1400 amino acids (Jafari et al. 2020; Avila Rodríguez, Rodríguez Barroso, and Sánchez 2018; Subhan et al. 2021). Collagen has a characteristic tertiary triple helix structure dominated by the X-Y repeats of glycine, where X is generally hydroxyproline, and Y is proline, which is associated with homo- or heterotrimeric (Figure 4a(right)) (Jafari et al. 2020). The presence of hydroxyproline in collagen is believed to contribute to its thermo-stability; mutations that suppress hydroxyproline at various points in the collagen sequence significantly decrease its thermal denaturation temperature (Abascal and Regan 2018). Glycine and alanine make up more than 50% of the amino acids in collagen, while proline and hydroxyproline make up about 20%. The presence of glycine is vital for the rotational freedom required to form the helical structure of collagen. This tertiary triple helix collagen structure assembles more complex supramolecular structures such as fibrils, beaded filaments, hexagonal networks, and anchoring fibrils (Coppola et al. 2020; Abascal and Regan 2018; Liu et al. 2019; Ocak 2018). Covalent bonds are formed between several collagen molecules in cross-sections to form collagen fibrils' basic units (Ahmed, Haq, and Chun 2019).

Gelatin

Gelatin is a biopolymer made from native collagen that has been denatured. It has comparable structures to collagen. Gelatin ensues from the partial acid or alkaline hydrolysis of animal collagen extracted from bovine (Cao, Wang, et al.

Table 2. Summary of current primary uses and applications of the inedible animal by-product and their extracted components.

Animal By-Products	Reprocessed Products	Major Uses	Ref
Bone	Extraction of collagen	Collagen, gelatin, and bone meal	(Irshad and Sharma 2015; Bah et al. 2013; ur Rahman, Sahar, and Khan 2014; Alao et al. 2017; Atef et al. 2020; He, Lan, et al. 2020; Sousa et al. 2020; Tan, Karim, et al. 2020; Kim, Ham, et al. 2020)
Skin, Hide	Cured hides and skin, textile, leather	Leather clothes, belts, household upholsteries, bags, footwear, drums, luggage, wallets, sports goods, gelatin, etc.	(Irshad and Sharma 2015; Rahman, Sahar, and Khan 2014; Bai, Wei, and Ren 2017; Atef et al. 2020; He, Lan, et al. 2020; Sousa et al. 2020; Tan, Karim, et al. 2020; Kim, Ham, et al. 2020)
Hair, Wool	Keratin extraction and textile	Keratin, cloth, carpet, matters, woven fabrics, and insulators, adhesive, biocomposites	(Scobie et al. 2015; Liu et al. 2013; Shavandi and Ali 2018; Shavandi and Ali 2019b, 2019a; Ramya, Thangam, and Madhan 2020; He, Xu, et al. 2020; Su et al. 2020; Ge et al. 2021; Tasaki 2020; Wang et al. 2018; Rajabinejad et al. 2018)
Organ, Gland	Medicinal and pharmaceutical	Heparin, enzymes, steroid, trypsin, insulin, estrogen, corticotrophins and progesterone	(Irshad and Sharma 2015; Rahman, Sahar, and Khan 2014; Alao et al. 2017; Grønlien et al. 2019; Vidal et al. 2020; Araújo et al. 2021; Schmidt et al. 2020; Saenmuang, Phothiset, and Chumnanka 2020; Mirzapour-Kouhdasht et al. 2019)
Horns, Hoof	Hoof and horns meal, extraction of keratin and collagen	Collagen, keratin, buttons, plates, fertilizer, glue, gelled food,	(Alao et al. 2017; Karjalainen et al. 2021; Purwaningsih and Triono 2019; Feroz, Muhammad, Ratnayake, et al. 2020; Pataridis, Romanov, and Mikšík 2019)
Blood	Pharmaceutical products and blood meal	Tennis strips, fertilizer, animal feed, stabilizer, emulsifier and blood pudding	(Irshad and Sharma 2015; Rahman, Sahar, and Khan 2014; Alao et al. 2017; De Boeck et al. 2018; Tabani et al. 2018)
Intestine	Sausage casting, suture, and musical instruments	Burn dressing, pet food, human food, meat meal, sausage, string for musical instruments	(Irshad and Sharma 2015; Alao et al. 2017),

2020), fish (Mahjoorian et al. 2020), and porcine (Rohman et al. 2020) connective tissues such as skin and bones (Al-Hassan 2020; Tan, Karim, et al. 2020; Kim, Ham, et al. 2020). By means of alkali or acid pretreatment, the triple-helical collagen structure is cleaved into single protein chains, and this reaction yields gelatin as a water-soluble hydrolysis product (Figure 4b). The triple-helical structure of collagen chains is changed to a random coil structure (helix-to-coil transition) in gelatin production using heat that destroys the hydrogen and covalent bonds. Therefore, the ensuing gelatin shows a lower molecular weight of polypeptides between 16 to 150 kDa. Gelatin consists of ~ 98-99% (by dry weight) protein and contains 18 amino acids, including eight of the nine amino acids essential for humans (Ahmad et al. 2019). Gelatin is water-soluble, and has the ability to form thermally reversible gels (Ahmad et al. 2019).

Keratin

After collagen, keratin is the most important structural biopolymer found in animal bodies (Chilakamarry et al. 2021). As depicted in Figure 4c (left), keratin has some similarities and differences with collagen. α -helix polypeptide chains of both proteins constitute a well-defined amino acid sequence that is made of smaller amino acid residues such as alanine and glycine. In collagen, three α -helices (tropocollagen) twist together to form the collagen fibril, while, in keratin, coiled-coil is formed with two polypeptide chains twisting together (α -keratin) (Figure 4c (right)) [54]. Keratin, unlike collagen, is a non-vascularized tissue because keratinocytes (keratin-producing cells) die after producing keratin (Chilakamarry et al. 2021; Reddy et al. 2021). Based on the sulfur content, keratin can be classified into two groups: a) hard keratin–with ~ 5% of sulfur content, which is found in hair, horns, nails, and feather and has high strength due to its high content of cysteine; and b) epidermal keratin with 1% of sulfur content, known as soft keratin (Nuutinen et al. 2019). β -helix and α sheet are two conformations that can be seen in the keratin (β -keratin and α -keratin). Even though both α -keratin and α -keratin are rich in cysteine and have large number of disulfide crosslinks, they are very different in their secondary and tertiary structures. β -keratin is a helical protein, which forms into coils and finally turns into helical filaments (Wang et al. 2021). β -keratin and -keratin in their functional form are usually incorporated into an amorphous matrix (Wang et al. 2021). °C -keratin exhibit other functions as well, such as the structure and color in birds' feathers (Qiu et al. 2020).

Silk fibroin

Silk is a natural protein mainly derived from *Nephila clavipes* and *Araneus diadematus* spiders, *Bombyx mori (B. mori)* domestic silkworms, *Antheraea pernyi,* and *Samia cynthia ricini* wild silkworms (Costa, Silva, and Boccaccini 2018b). Silk mainly comprises a core protein fibroin (72-81%) and its glue-like coating sericin (19-28%) (Figure 4d), and small amounts of fat, color, and ash (1.8-2.4%). Each silk fiber constituents of two silk fibroin filaments that are assembled from microfibrils and nanofibrils with a diameter of 20-200 and 3-5 nm, respectively (Ling et al. 2018).

Silk fibroin consists of two chains with different molecular weights; a heavy chain with a molecular weight of ~390 kDa and a light chain with terminal C and N groups with a molecular weight of > ~26kDa (Guo, Li, and Kaplan 2020). Silk fibroin chain structure presents a non-covalently

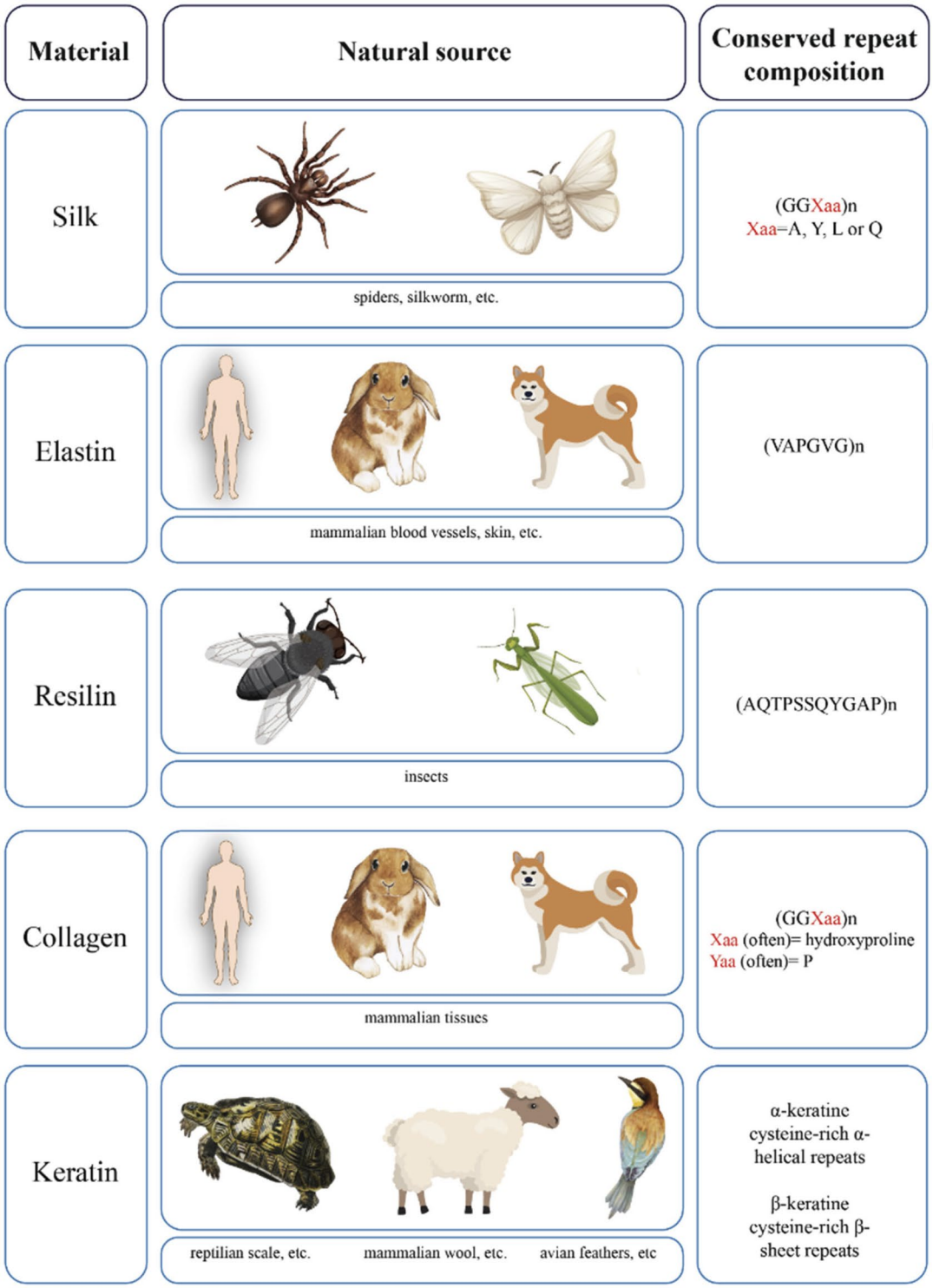

Figure 3. Natural sources and primary structures of common proteins extracted from animal by-products (Adapted from (Abascal and Regan 2018)).

Table 3. Distribution of the most common collagen types within mammalian tissues (Coppola et al. 2020; Bielajew, Hu, and Athanasiou 2020; Shulman et al. 2021; Senadheera, Dave, and Shahidi 2020; Kim, Kim, Yeon, et al. 2018; Zhang et al. 2018; Davis et al. 2020; Akram and Zhang 2020b).

Collagen type	Tissue	Application/ function in the human body
I	Bone, skin, ligaments, cornea	Membranes for guided tissue regeneration
II	Cartilage, vitreous body, nucleus pulposus, cornea, reticular fiber	Arthritis treatment and cartilage repair
III	Skin, vessel walls, reticular fibers of lungs, liver, spleen	Hemostats and tissue sealants
IV	Basement membranes	Enhancer for cell attachment and diabetic nephropathy indicator
VI	Cornea (often associated with type I collagen), dermis, lungs, cartilage, intervertebral disk, placenta	Hemostat

linked glycoprotein with a molecular weight of 27.7 kDa and provides integrity to the whole structure, which their molar ratio is 6:6:1(Nguyen et al. 2019). Silk is a large protein (approximately 200-350kDa or more) that interrupts repetitive modular hydrophobic domains of its structure by small hydrophilic groups (Figure 4d (right)). The hydrophobic domains are composed of glycine-x (45.9%), where "x" can be either alanine (30.3%), serine (12.1%), tyrosine (5.3%), or valine (1.8%) that transited into the β-sheet structure (Ma, Wang, and Dai 2018). In comparison, the random coils and helical structure are assembled by hydrophilic domains with alanine (14%), serine (10%), glycine (9%), and acetylated N-terminal. The random coil structure can be transformed into a structure of β-sheet by mechanical stretching and absorption of moisture (Ma, Wang, and Dai 2018). Different chemical groups such as amines, carboxyl, alcohols, and thiols make silk fibroin an ideal material for chemical modifications.

Sericin is made up of 18 amino acids, 70% of which are hydrophilic with an isoelectric point of around 4, allowing it to absorb considerable amounts of water while remaining partially soluble (Vickers 2017). The main configuration of sericin is amorphous (63%) that can easily change to the β-sheet by mechanical stretch and moisture absorption. Sericin, based on its molecular weight, solubility, and distance from silk fibroin is divided into three groups: type A is the outer layer and is soluble in water at a temperature of 60 >, type B is the middle layer and has the same solubility as type A, and type C is the innermost layer and is soluble in water at more than 83 > (Arango et al. 2021). The molecular weight of sericin has been reported to range from 10-400 kDa, depending on the extraction method, pH, temperature, and processing time (Arango et al. 2021).

Elastin

With a half-life longer than 70 years (Wen, Mithieux, and Weiss 2020), elastin is one of the most stable proteins. It has been shown that elastin positively influences cell growth, phenotype, adhesion, and proliferation (Wen, Mithieux, and Weiss 2020; Cabello et al. 2018). Elastin is synthesized by elastogenic cells such as smooth muscle, fibroblasts, and endothelial cells (Wen, Mithieux, and Weiss 2020). By encoding a single-copy ELN gene, these cells secrete tropoelastin, a water-soluble precursor of elastin comprising 65-70 KDa hydrophobic and hydrophilic domains (Wen, Mithieux, and Weiss 2020). Predominantly hydrophobic residues constitute valine, alanine, proline, and glycine, whereas lysine and alanine compose the hydrophilic domains. The insoluble elastin fibers are produced from tropoelastin through extensive cross-linking with the matrix (Wen, Mithieux, and Weiss 2020; Cabello et al. 2018), followed by oxidation by the lysyl oxidase. This enzyme oxidizes most of the lysine residues in tropoelastin to form further covalent crosslinks (Halabi and Mecham 2018). Four lysine residues from desmosine and isodesmosine are the

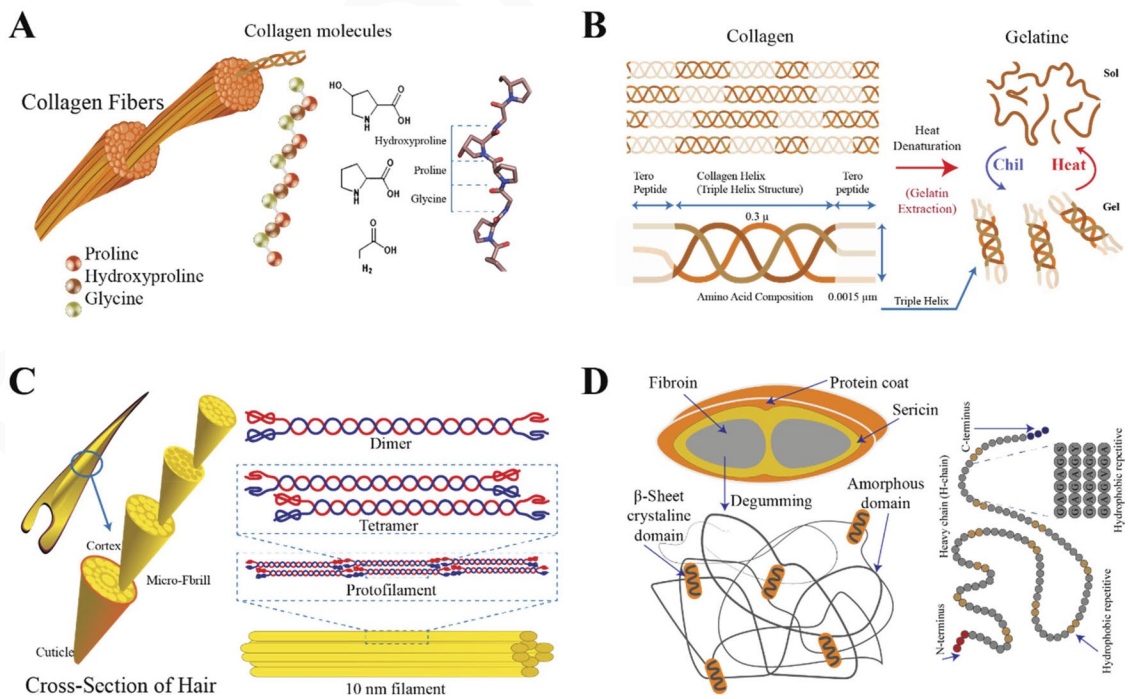

Figure 4. A) Collagen fibers, fibrils, and triple helix structure which are dominated by the glycine-proline-hydroxyproline repeats(left), collagen amino acid chains structure (right) (Adapted from (Jafari et al. 2020)), B) Transformation of the triple-helical structure of collagen chains into the gelatin chain by using heat (Adapted from (Kaewdang 2014)), C) microfibril, intermediate filament, and coiled-coil of two α-helixes structure of keratin (left) (Lee et al. 2014) and schematic representation of the coiled-coil structure of keratin, the anti-parallel orientation of two dimers join side-by-side, two protofilaments intertwine to form protofibrils (right) (Adopted from (Banerjee et al. 2014)), and D) schematic represents two fibroin fibers of silkworms are covered by sericin, and an amorphous matrix containing β-sheet crystallite of silk fibroin fibers (left), and schematic represents hydrophobic and hydrophilic domains of the heavy chain of silk fibroin (right) (Adapted from (Jao, Mou, and Hu 2016)).

major crosslinks in elastin. Other less frequent crosslinks in elastin are lysinonorleucine, and allysine aldol (as shown in Figure 5) (Halabi and Mecham 2018).

Pretreatment, extraction, recovery, and purification of common animal by-products proteins

The process of producing proteins from animal by-products is divided into four main stages, and the quality of the extracted proteins highly depends on the performance of these steps: preparation, pretreatment, extraction, recovery, and purification (Jafari et al. 2020). Although some pretreatment and extraction methods are similar for all animal by-product proteins, usually the method can vary depending on the target protein. Summary of extraction methods for proteins documented in the literature is listed in Table 4.

Collagen and gelatin pretreatment and extraction

Non-collagen components should be eliminated before extracting collagen from animal by-products. Some pretreatment processing like swelling, degreasing, demineralization, and degreasing are used for this purpose. Using alkali treatment with NaOH, raw materials swells and the non-collagen components are removed. Although NaOH concentration and solvents temperature can be varied based on the raw materials and degree of collagen crosslinking, it has been reported to prevent using a concentration higher than 0.5 – 1 M NaOH at the temperature of 4 to 20 °C to avoid damage to the collagen structure. Hydrochloric acid and EDTA are used to demineralize the collagen, which is a key step in the extraction process. At the same concentration of hydrochloric acid and EDTA, EDTA showed better decalcification than hydrochloric acid from animal bones and fish scales. Ethanol, n-hexane, and ethyl ether are used to remove the fats. It has been reported that the effect of the pretreatment method on the degree of hydrolysis of bovine collagen was significant so that the effectiveness trend of treatment methods was Boiled > high preussure > untreated (Zhang et al. 2013). New techniques such as high pressure, microwave, ultrasound, and pulsed electric fields can also assist traditional collagen pretreatment methods Q2 (Chotphruethipong, Aluko, and Benjakul 2019a, 2019b). The cavitation produced by a high frequency of ultrasound irradiation can damage raw materials and break them into smaller pieces, so the contact area for protein extraction increases (Zou et al. 2020a). The shear rate produced by cavitation bubbles is inversely proportional to their size, so when the higher ultrasonic frequency is applied, the shear rate increases while the length of the bubbles decreases (Figure 6c (right)) (Zou et al. 2020a; Ojha et al. 2020). Boiling and high-pressure pretreatment influences the degree of hydrolysis of bovine collagen, with boiling having a higher efficacy than high pressure (Hong et al. 2019).

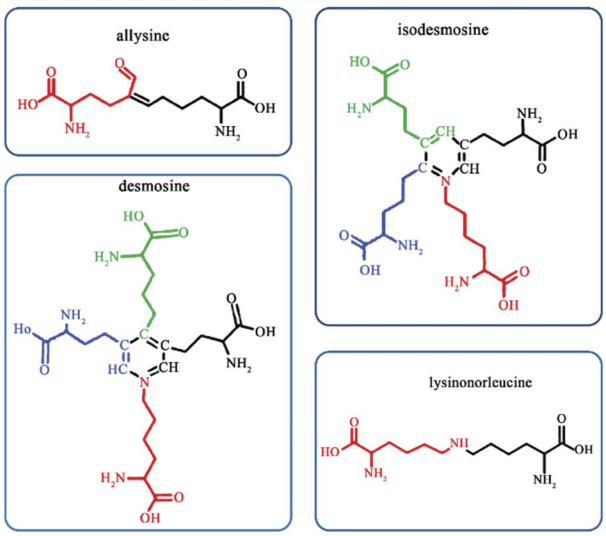

Figure 5. The chemical structures of crosslinking elastin's amino acids: tetra functional desmosine, isodesmosine, allysine, and lysinonorleucine (Adapted from (Schräder et al. 2018)).

Enzymatic hydrolysis is the most common method for collagen extraction, as it is a mild reaction with minimum side effects and minimal damage to the structure of the extracted protein (Jin et al. 2019). The use of pepsin as an enzymatic pretreatment agent allows for the cleavage of the telopeptide regions of the triple helix, which is called pepsin soluble collagen (PSC). Consequently, pepsin facilitates the leaching of collagen peptides in solution and eventually increases the extraction yields (Grønlien et al. 2019). Trypsin, papain, alkaline protease, bromelain, pancreatin, and lactase are some of the other enzymes that have been used to extract collagen. Factors such as type of enzyme, enzyme concentration, hydrolysis time, and the ratio of solid to liquid (S/L) affect the enzymatic extraction process. The degree of hydrolysis of bovine collagen with various enzymes has been reported to be as follows: alcalase > collagenase °C proteinase °C trypsin ≈ thermolysin $(NH_4)_2SO_4$ pepsin (Zhang et al. 2013).

The second common method for collagen extraction is chemical hydrolysis like acid, alkali, and salt, which are cheaper and more straightforward than enzymatic hydrolysis (Dhakal et al. 2018). Acid-soluble collagen (ASC) (Figure 6a) is a method to demineralize and extract collagen at low temperatures by using organic or inorganic acids. Organic acids have a higher extraction rate than inorganic acids. Acid breaks the inter and intramolecular bonds present in the collagen helix and enhances the extraction efficiency, acids can depolymerize the heavy-weight proteins into shorter peptides. Hydrochloric acid and acetic acid are often used for collagen extraction (Jafari et al. 2020; Coelho et al. 2017; Noorzai et al. 2019; Chinh et al. 2019). The acid concentration is crucial in the production of ASC, and it typically varies from 0.5 to 1 M. This acid concentration must break inter and intramolecular crosslinks while not affecting the collagen chain structure (Blanco et al. 2019; Bai, Wei, and Ren 2017). A small negative effect on the yield was observed when the acetic acid concentration was the highest (1.05 M) caused by undesirable side reactions such as a change in the collagen chain structure (Meng et al. 2019). Other parameters

Table 4. Summary of "Extraction methods for proteins," documented in the literature.

Composition	Waste sources	Extraction Type	Solvent/Enzyme	Pretreatment, extraction parameters and yield (Y)	Remarks	Ref
Collagen	Giant croaker, (Nibea japonica)	PSC	Pepsin	S/L = 1:60 Time = 8.5 h T = 4 °C AcOH = 0.5 M Pepsin = 1389 U/g, Y = 84.85%	triple-helical structure of psc zqs reserved.	(Coelho et al. 2017)
	Bull, calf, cow, face-pieces, and ox-hides	ASC, PSC, and modified acid-enzyme solubilization (MAPSC)	Acetic acid Pepsin	Y = 75.13% MAPSC, 74.45% PSC, and 3.80% ASC	MAPSC was inefficient for collagen extraction	(Noorzai et al. 2019)
	Carp Fish Scale	ASC	Acetic acid	AcOH = 0.5 M T = 4 °C Time = 48 h Y = 13.6%	collagen contains 18 amino acids with tryptophan	(Chinh et al. 2019)
	Turkey tendon	ASC and PSC	Acetic acid and pepsin	AcOH = 0.5 M T = 4 °C Time = 48 h	Collagen type I and III with preserved native triple helix. High thermal stability	(Grønlien et al. 2019)
	Codfish skins	DES extraction	ChClOA (oxalic), ChCl-HAC (acetic), ChCl-La (lactic), ChCl-EG (ethylen glycol), and ChCl-G (glycerol), as well as ChCl-U (urea)	T = 25-75 °C Time = 1-7 h L/S = 60:1-160:1 Y = 11.45-99%	extraction abilities: ChClOA > ChCl-HAC > ChCl-La > ChCl-EG > ChCl-G > ChCl-U,	(Bai, Wei, and Ren 2017)
	clown featherback (Chitala ornata) skin	ASC and ultrasound	Acetic acid	AcOH = 0.5 M S/L = 1:15 Time = 48 h T = 4 °C Frequency = 20 kHz Ultrasound treatment time = 10-30min Y = 23.46-57.35%	By increasing ultrasonication time yield of collagen increased	(Petcharat et al. 2021)
	Nile tilapia skin (Oreochromis niloticus)	ASC	Acetic acid	AcOH = 0.35-1.05 M Time = 31-65 h T = 4-20 °C Y = 13.5-19%	Lower acid concentration and higher temperature and time obtained better yield. Higher temperature and time maintained triple helix integrity	(Menezes et al. 2020)
	P. olivaceus skin	PSC	Pepsin	AcOH = 0.5 M Pepsin = 1:100 Time = 24 h T = 4 °C Y = 29.30%	increasing collagen yield without damaging to the its structure	(Chandika et al. 2021)
	lamb and sheep by-products	PSC	Pepsin	AcOH = 0.5 M Time = 3 days T = 4 °C Y = 18% lamb and 12.5% by-products	collagen type I and an M_W between 100 and 5 kDa.	(Vidal et al. 2020)
	Chicken sternal cartilage	PSC and ultrasound-PSC	Pepsin	AcOH = 0.5 M Time = 96 h T = 4 °C Frequency = 20-25 kHz Ultrasound treatment time = 36 min Y ≅ 40-80%	Ultrasound treatment time changed secondary structure of collagen	(Akram and Zhang et al. 2020c)
	Chicken feet	ASC and PSC	Acetic acid and pepsin	AcOH = 0.5 M Time = 24 h S/L = 1:10 (w/v) T = 4 °C		(Araújo et al. 2021)
	Sturgeon fish skin	ASC and PSC	Acetic acid and pepsin	AcOH = 0.5 M Time = 48 h T = 4 °C Pepsin = 20 $U.g^{-1}$ S/L = 1:15 Y = 9.98% ASC, and 9.08% PSC	collagen type I, Glycine content was 21.14% and 21.58% for ASC and PSC, respectively.	(Atef et al. 2020)

(Continued)

Table 4. (Continued).

Composition	Waste sources	Extraction Type	Solvent/Enzyme	Pretreatment, extraction parameters and yield (Y)	Remarks	Ref
	Pig skin	PSC	Pepsin	AcOH = 0.5 M pH = 2.2 T = 4 °C Time = 18 h	The initial enzyme concentration has a significant effect on immobilization.	(He, Lan, et al. 2020)
	Tilapia and Gray mullet scales	ASC	Acetic acid	AcOH = 0.5 M T = 4 °C Time = 3 days Y = 40%	all the extracted collagens have inhibitory activity	(Shalaby et al. 2020)
	Atlantic cod (Gadus morhua) skins	Supercritical fluids technology	CO_2	T = 37 °C P = 50 bar Time = 3 h Y = 13.8%	Supercritical fluids technology is an environmentally sustainable process	(Sousa et al. 2020)
	Chicken lung	PSC and ultrasound-PSC	Pepsin	Pepsin = 2000 (U. g^{-1}) Time = 5-50 h AcOH = 0.5 M Ultraound power = 0-200 W Max yield = 31.25%	collagen containing more imino acid has more thermal stability	(Zou et al. 2020a)
	Chicken meat residue	PSC	Pepsin	AcOH = 0.5 M Pepsin α 400 S/L = 1:15 (w/v) Time = 3 days T = 4 °C	The degree of hydrolysis was obtained using Alcalase was 36.11%, and Flavourzyme was 12.02%.	(Schmidt et al. 2020)
	Fringescale sardinella (Sardinella fimbriata) waste	ASC and PSC	Acetic acid and pepsin	AcOH = 0.5 M Time = 30 and 36 h T = 4 °C Y = 7.48% ASC and 0.96% PSC	no remarkable difference between collagen extracted by ASC and PSC	(Hamdan and Sarbon 2019)
Gelatin	Camel skin (Camelus dromedarius)	Thermal and chemical pretreatment method	Distilled water	$Ca(OH)_2$ = 1.3 M Ammonium sulfate = 4% $Time_{P*}$ = 48 h T_P* = 25 °C Time = 5 h T = 75 and 90 °C Y = 36.8-42.4%	Gel bloom was 72.08–122.87 g, melting point 18.4–21.6 °C and a gelling point 15.2–11.1 °C.	(Al-Hassan 2020)
	Black tilapia skin	Water extraction	Citric acid and water	NaOH = 0.5 M $Time_P$ = 4 h T_P = 25 °C Citric acid = 0.3 M T = 45, 55, 65, and 75 °C Time = 12 h Y = 10.79, 11.52, 14.91, and 18.27%	Increasing the gelatin yield by temperature	(Tan, Karim, et al. 2020)
	Duck skin	Water bath extracting method	tap water	T = 60 °C Time = 10min Y = 11.71%	Assessment to the highest gelatin yield with the superheated steam extraction method	(Kim, Ham, et al. 2020)
		Sonication extraction method		T = 60 °C Time = 10min Frequency = 40 kHz Y = 26.15%		
		Superheated steam extraction method		T = 150 °C Time = 10min Y = 44.02%		
		Microwave extraction method		Frequency = 2450 MHz Power = 200W Time = 10min Y = 28.51%		
	Camel skin	Water extraction	water	Sulfuric $acid_P$ = 0.1 M $Time_P$ = 3 days T_P = 10 °C Time = 3-5 h T = 50 °C Y_{max} = 29.1%	The maximum gelatin yield from camel skin was obtained at 71.87 °C and pH 5.26 after 2.58 min.	(Kim, Ham, et al. 2020)
	Black-bone and skin chicken by-products	Water extraction	Water	$NaOH_{P1}$ = 0.025, 0.050, and 0.075 N $Time_{P1}$ = 80 min T_{P1} = 22 °C Sulfuric $acid_{P2}$ = 15% (v.v^{-1}) $Time_{P2}$ = 40 min Time = 15 h T = 40 °C Y = 9.53-10.59%	The NaOH concentration did not show a strong effect on the physicochemical properties of gelatins.	(Saenmuang, Phothiset, and Chumnanka 2020)

(Continued)

Table 4. (Continued).

Composition	Waste sources	Extraction Type	Solvent/Enzyme	Pretreatment, extraction parameters and yield (Y)	Remarks	Ref
	Bovine bone	Water extraction	Water	$AcOH_P = 0.05$ M Hydrochloric $acid_P = 0.05$ M Citric $acid_P = 0.05$ M $Time_P = 26$ h $T_P = 25$ °C T = 70 °C Time = 7 h pH = 5 Y = 4.25-11.75%	citric acid disrupted more collagen structure than acetic acid and hydrochloric acid	(Cao, Wang, et al. 2020)
	Crap by-products	Water extraction	Water	(1) Ultrasound $assisted_P$ $Power_{P1} = 50$, 100, and 150 W $Time_{P1} = 5$, 24, and 45 min $T_{P1} = 50$ °C Y = 19.80-27.00% (EC-Europa) Microwave $assisted_P$ $Power_{P2} = 350$ W $Time_{P2} = 1$,3, and 5 min Time = 2 h T = 60 °C Y = 0.82-1.27%	Yield of microwave was lower than ultrasound pretreatment	(Mirzapour-Kouhdasht et al. 2019)
Keratin	Red sheep's hair	Alkali and reduction	Aqueous solution	Sodium sulfide = 0.125M Time = 4 h T = 40 °C Y = 54.98% Sodium hydroxide = 0.5N Time = 3 h T = 60 °C Y = 57.78% Urea = 8 M Cysteine = 0.165 M Time = 5 h T = 75 °C Y = 64.52% Urea = 8 M SDS = 0.26 M Mercaptoethanol = 1.66 M T = 50 °C Time = 12 h Y = 88.96% Urea = 8 M Sodium metabi sulfite = 0.5 M Time = 2 h T = 65 °C Y = 77.42% Urea = 8 M Sodium metabi sulfite = 0.5 M SDS = 0.1 M T = 65 °C Time = 12 h Y = 96%	MW of obtained keratin was 40-60 kDa	(Ramya, Thangam, and Madhan 2020)
	Poultry feathers	Reduction	Distilled water	Mercaptoethanol = 1.168 mL Urea = 31.89 g Time = 48 h T = 70 °C Sodium sulfite = 10 g Urea = 31.89 g Time = 48 h T = 70 °C Sodium sulfite = 10 g SDS = 5 g Urea = 31.89 g Time = 48 h T = 70 °C	All the methods have antioxidant potency.	(Alahyaribeik and Ullah 2020)

(Continued)

Table 4. (Continued).

Composition	Waste sources	Extraction Type	Solvent/Enzyme	Pretreatment, extraction parameters and yield (Y)	Remarks	Ref
	Wool	Reduction	Water/ ethanol co-solvent	SDS = 2.5 g L-cysteine hydrochloride = 2.5 g Na_2SO_3 = 1 g Ethanol 70% = 100 mL T = 50 °C for 1 h and 65 °C for 2 h Y = 67%	ethanol destroyed partial hydrogen bonds and hydrophobic interactions.	(He, Xu, et al. 2020)
	Wool	Enzymatic	Water	Keratinase = 100,000 U Time = 48 h T = 50 °C	MW of keratin was approximately 45 and 28 kDa	(Su et al. 2020)
	Rabbit hair	Reduction	Water	Urea = 8 M L-cysteine = 0.165 M pH = 11 Time = 5 h T = 85 °C Y = 61%	L-cysteine was used as a reduction agent	(Ge et al. 2021)
	Hog hair	Thermal hydrolysis process	water	Deionized water = 1 L Heating rate = 3 °C.min^{-1} T = 100-220 °C Time = 1 h Pressure = equal to the saturated water vapor pressure at any given temperature Y = 70%	MW was from 10-100 kDa	(Tasaki 2020)
	Feathers chicken	Microwave and ultrasound irradiation	Water and water/ ethanol	Microwave Power = 960 W Frequency = 2450 kHz Time = 5, 10, and 15 min T = 70 °C Ultrasound Power = 3.8 W Frequency = 45 kHz Time = 5, 10, and 15 min T = 70 °C	The microwave irradiation promotes the growth of the beta-sheet over the alpha helix.	(Rodríguez-Clavel et al. 2019)
	Poultry feathers	DES	Aqueous DES	NaOAc: urea = 1:2 and 1:3 ChCl: urea = 1:2 as a reference solution Time = 2-24 h T = 80-100 °C Y = 45%	86% of the feathers were dissolved	(Nuutinen et al. 2019)
	Rabbit hair	DES	DES solution	ChCl: oxalic acid = 1:2 T = 80-120 °C Time = 2 h	MW ranging was from 3.8 to 5.8 kDa with a high proportion of serine, glutamic acid, cysteine, leucine, and arginine.	(Wang et al. 2018)
	Wool	Oxidative	Aqueous solution of 2% w/v peracetic acid	Peracetic acid = 2% (w/v) Time = 24 h T = room temperature Y = 31%	Keratin extracted with oxidative, characterized by stronger ionic interaction and higher molecular weight, is the most temperature stable keratin.	(Rajabinejad et al. 2018)
		Redaction	Aqueous solution	Tris = 0.5 M DTT = 0.14 M EDTA = 6 mM Time = 2.5 h T = 25 °C Y = 29%		
		Sulfitolysis	Aqueous solution	Urea = 8 M Sodium metabisulfite = 0.5 M NaOH = 5 M T = 65 °C Time = 2.5 h Y = 32%		
		Superheated water hydrolysis	Superheated water	T = 170 °C Time = 30 min Y = 31%		

(Continued)

Table 4. (Continued).

Composition	Waste sources	Extraction Type	Solvent/Enzyme	Pretreatment, extraction parameters and yield (Y)	Remarks	Ref
	Feathers	Ionic liquids + ultrasound irradiation	Solution A	Potassium iodide = 0.4 M Sodium hydroxide = 0.05 M Ammonium heptamolybdate tetrahydrate = 1.6 α 10^{-4} Power = 100, 200, and 280 W Frequency = 20 kHz	Improved dissolution of feather waste by ultrasound technology.	(Azmi, Idris, and Yusof 2018)
			Solution B	Potassium hydrogen phthalate = 0.1 M Power = 100, 200, and 280 W Frequency = 20 kHz		
Silk	Silk cocoon	Enzymatic + ultrasound irradiation	Pancreatin, protease, papain, or bromelain	NaOH = 0.1-1.0N Power = 750 W Amplitude = 80% Pulse = 20 s/20s T = 25 °C Enzyme = 0.5% (w/v) pH = 7.0 Time = 3-24 h Y = 12.83-81.48%	Ultrasound treatment decreased solvent use and increased silk yield. MW of Silk peptide was <5 kDa.	(Eom et al. 2020)
	B. mori cocoon	DES	DES solution	ChCl: LA = 1:1 Time = 30 h ChCl: MA = 1:1 Time = 50 h T = 100 °C	DESs increased the swelling of silk fibers	(Tan, Wang, et al. 2020)
	B. mori cocoon	Ionic liquid	Choline based ionic liquid	Time = 15 min-6h T = 40, 50, and 60 °C Choline hydroxide aqueous solution = 46% w/w	The optimized conditions were T = 50 °C for 2 h to achieve maximum dissolution, i.e. 25%.	(Samie et al. 2020)
	B. mori cocoon	Organic solvent	Acetone	Na_2CO_3 = 2% (w/v) Time = 2 h T = 80 °C LiBr = 9.3 M Silk fiber: acetone = 1:3 and 1:8 T = 50 °C	Acetone decreased the dialysis time	(Wang, Zhang, and Wei 2020)
	Eri silk	Water	Distilled water	Marseilles soap = 10 g.L^{-1} Sodium carbonate = 1.5 g. L^{-1} Time = 30-120min Pressure = 0 and 103 kPa	Alkali method for silk degumming had the most effect, especially when pressure cooked at 103 kPa. During soap and water, degumming led to incomplete sericin removal.	(Oduor et al. 2020)
		Soap Alkali	Marseilles soap Sodium carbonate			
	B. mori	Hot water	Deionized water	T = 120 °C Time = 30 min	the crystalline index and crystallite diameters were found 39.66% and 2.179 nm, respectively	(Saha et al. 2019)
Elastin	Raw hide trimming wastes	Thermo-chemical treatment method	Alkali solvent	Water = 300% Lime = 10% NaOH = 5% NaCl = 5% Shaking for 8 h/ day for 7 days	The denaturation temperature was 275 °C	(Yoseph et al. 2020)
	Broiler skin	Hot alkali	Alkali solvent	NaCl = 1 M Time = 24 h NaOH = 0.1 M Time = 15 min T = boiling water bath	The extracted elastin showed antioxidant activity.	(Nadalian et al. 2019)

*Index P means pretreatment, and S/L means the ratio of solid to liquid.

that influence the yield of collagen extraction in this process are temperature, time, and S/L. A synergistic interaction between these parameter has been illustrated for yield of Nile tilapia collagen. By increasing in extraction time from 45 h to 65 h and temperature from 4 °C to 20 °C, the yield increased from 15.3-19% (Menezes et al. 2020). The alkaline extraction method, due to collagen denaturation, low yield, and poor performance, has rarely been employed alone and is often combined with acid and enzyme methods (Meng et al. 2019). ASC and PSC were used and compared for collagen extraction from surf clamshell (*Coelomactra antiquata*) by Wu et al. (Wu et al. 2019). Their collagen extraction yield for ASC was 0.59% and for PSC was 3.78%. In another study, the effects of operating parameters such as acetic acid concentration, pepsin content, and time of the enzymatic hydrolysis on the yield of collagen extraction from chicken feet have been determined. Although collagen yield increased by increasing pepsin content, the yield of extracted collagen had an inverse result by increasing hydrolysis time. The highest collagen yield (72.98%) was obtained when the acetic acid was 0.7 M pepsin 0.2%, and hydrolysis time 12 h (Araujo et al. 2018).

Acid extraction methods are the most used approaches for collagen extraction. However, high acidity, high energy consumption, prolonged processing time, limited a low extraction yield, and high temperature could adversely influence the final product, resulting in increased solubility, bitterness, nutritional loss, and poor functionality. Combining ultrasonic electric fields with acidic and enzymatic extraction methods increases the collagen extraction yield in a short time. The utilization of ultrasound for 36 min improved the collagen extraction from chicken sternal cartilage from 32% to ~ 85%, and it was founded that an increase in sonication time increased the yield (Akram and Zhang 2020a). One of the latest techniques is using of deep eutectic solvents (DES), which is a mixture of two compounds, hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) (Amani et al. 2021). Figure 6b (top) shows the HBA, and HBD structure used to separate aromatic-aliphatic hydrocarbons azeotropic by DES method (Gouveia et al. 2016; Li et al. 2016). Common DES components are based on choline chloride, oxalic acid, urea, and ethylene glycol, which are low toxic, biodegradable, low cost, and readily available (Bai, Wei, and Ren 2017; Florindo et al. 2014). DES-based methods have been employed in various areas of chemistry, such as metal dissolution, material chemistry, organic synthesis, electrochemistry, and enzyme reaction. Furthermore, recently, newer applications of DES have been uncovered based on the interaction between HBD and HBA that provide unique insight for the extraction and separation of bioactive components, including lignin, flavonoids, DNA, phenolic acid separation, as well as extraction of collagen peptides (Bai, Wei, and Ren 2017; Duan et al. 2016; Alvarez-Vasco et al. 2016). Bai et al.(Bai, Wei, and Ren 2017) used six different varieties of DESs to extract collagen peptides from cod skin. Figure 6b (bottom) shows a schematic of the interaction between the choline chloride-oxalic acid with collagen peptides. Such extraction system results in higher efficiency (91-93%) and purity (96-100%) compared to other solvents and hence was selected as optimal isolation solvent (Bai, Wei, and Ren 2017).

Another extraction method for the isolation of proteins from by-products is supercritical fluid extraction (SFE) which has several advantages: higher extraction yield, lower environmental effect, better fractionation, and improved selectivity compared to traditional extraction processes like ASC and PSC (Sousa et al. 2020). Although SFE is an environmentally friendly method, it may lead to changes in extracted protein structure(Hung, de Kok, and Verbeke 2016). Sousa et al. extracted collagen from Atlantic cod skins using acidified water with CO_2 (Figure 6c (left)), and the yield was reported as 13.6% (Sousa et al. 2020).

Finally, despite the drawbacks, such as low yield, long processing time, the toxicity of solvents, denaturation of protein during extraction, and poor performance, enzymatic and acidic extraction methods are still the most commonly used methods for collagen extraction. However, combining traditional techniques with pretreatment methods has increased their effectiveness; there are still many obstacles and difficulties. Pulsed electric field, ultrasound, high hydrostatic pressure, microwave, SFE, and DES introduced many advantages for extraction but can be combined with traditional methods to be more efficacious (Cao et al. 2021).

Keratin pretreatment and extraction

Unlike collagen, the complex 3 D structure of keratin requires chemical conditions to reduce or oxidize disulfide bonds, allowing for its dissolution and extraction (Shavandi, Silva, et al. 2017). The various inter and intra-molecular chemical bonds of keratin that increase the stability and strength of this molecule are illustrated in Figure 7a. Over the last years, several methods have been reported to extract keratin from animal by-products, classified into two main categories: protein denaturation and protein degradation (Shavandi, Silva, et al. 2017). Methods based on denaturation are divided into reductive, oxidative, and solphitolysis and extraction methods based on degradation are divided into alkaline, ionic liquid, enzymatic and microbial (Vineis et al. 2019). Table 5 shows the relative advantages, disadvantages, and applications of the extraction methods for keratin. Due to the high content of cysteine linkages and hydrophobic amino acids, it is difficult to dissolve keratin in a single polar or nonpolar solvent (Costa, Silva, and Boccaccini 2018a).

All methods based on the denaturation of keratin employ chemicals, surfactants, and denaturing agents, which have a crucial role in extraction, that can break down disulfide bonds without degrading the keratin chain or decreasing the molecular weight. At first, denaturing agents and surfactants increase the wettability and swelling of the keratin source by breaking the hydrogen and weakening of hydrophobic bonds between the protein chains, respectively. Step two involves breaking the disulfide bonds with a chemical that are classified as oxidative, reductive, and sulphitolysis based on their reaction mechanism (Vickers 2017). Guanidine or urea is the most common denaturing agent for increasing the keratin solubility in water, which facilities the reducing agents' functionality.

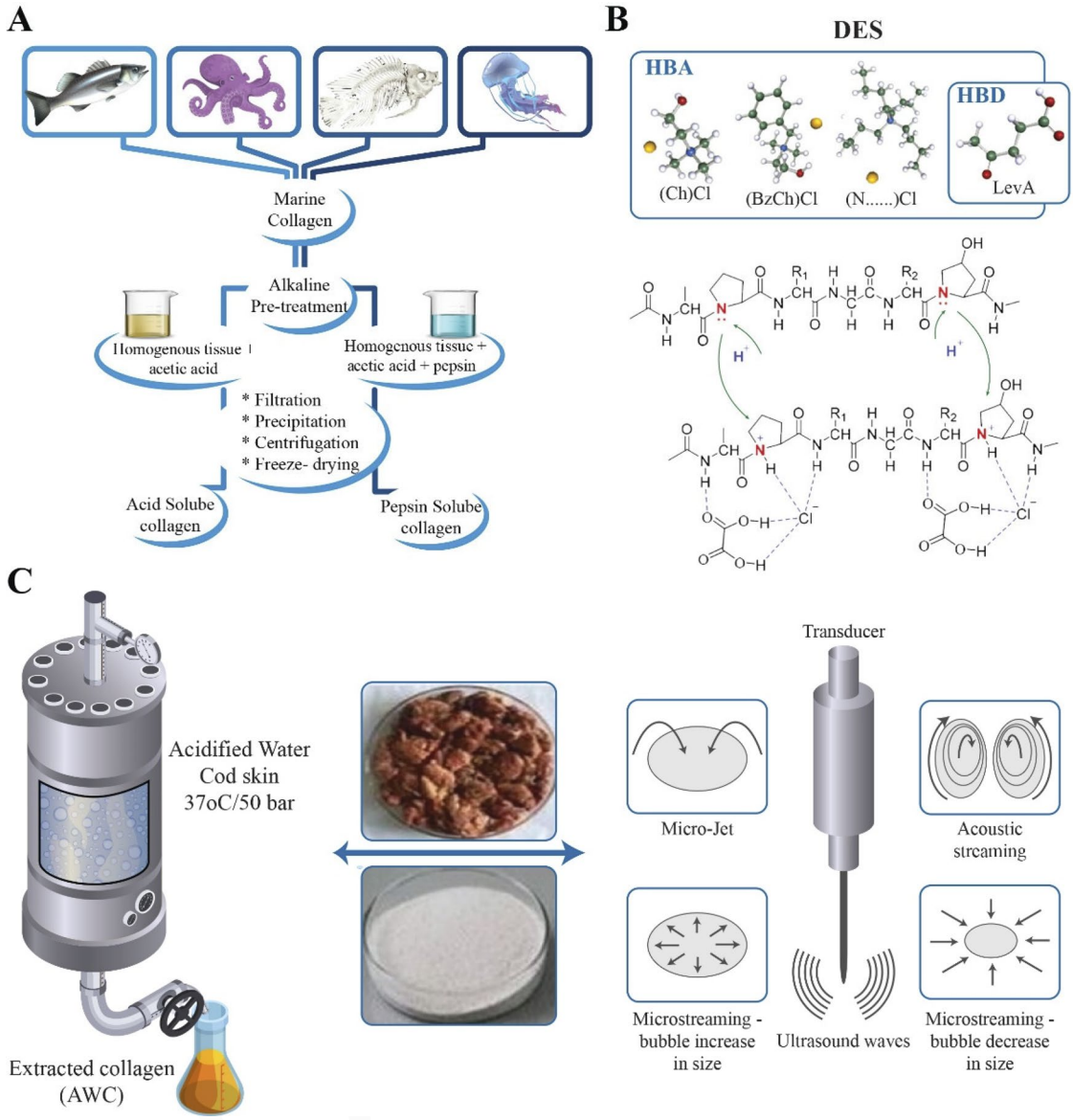

Figure 6. A) Similarities and differences between the acid-soluble collagen (ASC) method and the pepsin-soluble collagen (PSC) extraction method (Adapted from (Jafari et al. 2020)), B) Examples of the structure of hydrogen bond acceptors (Amani et al. 2021) and hydrogen bond donors (HBD) used at deep eutectic solvent method (Cholinium Chloride, [Ch]Cl, BenzylCholiniumchloride, [BzCh]Cl, and Tetrabutylammonium chloride, [N4444]Cl as HBA as well as levulinic acid, LevA as an HBD) (top) (Adapted from (Gouveia et al. 2016)), and schematic the reaction process between choline chloride – oxalic acid with cod skin collagen peptide (bottom) (Adapted from (Bai, Wei, and Ren 2017)), C) Schematic showing acidified water with CO_2 which is used for extraction of collagen (left) (Adapted from (Sousa et al. 2020)), and (f) Schematic illustration of the ultrasound-assisted extraction process and the bubble cavitation phenomenon involved in this extraction technique (right) (Adapted from (Zou et al. 2020b)).

However, the performance of the surfactants depends on their interactions type with keratin that can be changed from source to source or structure to structure (tertiary or secondary); anionic surfactants are more effective than cationic and neutral surfactants. Some studies have found that the utilization of sodium dodecyl sulfate (SDS) as a keratin surfactant increases the extraction rate (Shavandi, Silva, et al. 2017; Chilakamarry et al. 2021). The value of SDS that remains in the final products has been proved to be nontoxic (Shavandi, Silva, et al. 2017; Chilakamarry et al. 2021). The reduction mechanism is a two-step nucleophilic displacement reaction in which two reduction agents produce kerateines. 2-mercaptoethanol, thioglycolic acid, and dithiothreitol have been used as reducing agents. Temperature, incubation time, reduction agent ratio, and mass of the keratin source have been found to effect on the rate of keratin extraction from chicken feather (Table 4) (Kamarudin et al. 2017). Moreover, because keratin decomposes at pH greater than 11, most reduction extraction methods are carried out at alkaline conditions. Mercaptoethanol is often used in the reduction process but is undesirable due to its unpleasant odor, it is expensive, and is also toxic (Shavandi, Silva, et al. 2017; Shavandi, Carne, et al. 2017; Chilakamarry et al. 2021).

To break the disulfide bonds of keratin into cysteic acid residues, peracetic acid and performic are commonly used (Shavandi, Carne, et al. 2017; Donato and Mija 2019). Keratin extracted by oxidation methods can be divided into

Table 5. Advantages, disadvantages, and applications of the extraction methods for keratin (Shavandi, Silva, et al. 2017; Alahyaribeik and Ullah 2020; Eslahi, Dadashian, and Nejad 2013; Agarwal et al. 2019; Ji et al. 2014; Ramya, Thangam, and Madhan 2020).

Method	Advantage	Disadvantage	Application
Mechanical extraction	Simple process, low cost, high efficiency	High cost equipment requirements, high energy consumption, not easy to control	Animal feed
Reduction	Mild conditions, high keratin yield, large molecular weight	Complicated operation process, unstable keratin solution	Spinning; adsorbent
Oxidation	Simple process, low pollution	Low molecular weight	Animal feed
Acid/alkali hydrolysis	Simple process, small damage to cystine	Causing amino acid loss, corrosion equipment, secondary pollution, not easy to control	Animal feed, leather auxiliaries
Enzymatic hydrolysis	Mild conditions, environmentally friendly	Higher costs	Food packaging film, cosmetics, biomedical materials
Microwave irradiation	Short operation time, environmentally friendly, small side reaction	Low molecular weight, causing amino acid loss	Biomedical materials, fertilizers
Ionic liquid extraction	Low vapor pressure, high ion conductivity, non-flammability, high thermal stability, high solvation for specific solutes, and nonvolatility	Potentially toxic, higher costs, poor biodegradability, complex process, poor keratin spinnability, not soluble in water, difficult isolation	Protein fiber blended membrane, regenerated keratin fiber
Deep eutectic solvent (DES)	Green, environmentally friendly, biocompatibility, simple process, low cost, less time-consuming method, a low vapor pressure, relatively wide liquid-range, non-flammability, easy isolation	High viscosity	Biomedical applications

α-, β- and γ-keratose, which are soluble in specific range of pH. Therefore, after extraction, they can be separated from one another (Chilakamarry et al. 2021). Other method that can be used to break disulfide bonds is sulfitolysis, including the use of sodium sulfide ($NaSO_3$), sodium disulfite (NaS_2O_5), and sodium bisulfite ($NaHSO_3$), which are major sulfites that exist in aqueous solution (Shavandi, Silva, et al. 2017; Chilakamarry et al. 2021). Cysteine thiol and S-sulfonated are produced by sulfitolysis of a cysteine and S-sulfonated residue (Shavandi, Silva, et al. 2017). Sulfite ions concentration enhances with a pH increase up to 9, making the sulfitolysis reaction faster than bisulfite ions. To cleave disulfide bonds in wool, *Li* et al. (Li et al. 2019) used a new organic phosphonic compound named LKS-610, (Figure 7b). Based on the results from the valence state of the sulfur element on the fiber surface, they observed that when disulfide linkages bonds with the LKS-610 reagent, thiol groups are formed. The mass percentage of cysteine in wool fibers treated for 60 min at 80 ≈ was reduced from 10.09% to 1.05%, showing that most disulfide bonds were cleaved.

Alkaline extraction is an irreversible method that employs hot and alkali solutions to break amide bonds and convert them to amino acids like cysteine (the main amino acid in keratinous) (Shavandi, Silva, et al. 2017). A high concentration of alkaline solution can separate the hydrogen from sulfate and carboxylic groups. The solubilization of wool is improved under such conditions (Shavandi, Silva, et al. 2017); however, the peptide chains could be damaged. The breakdown of peptide chains forms the alkaline sulfide during the treatment process, which has a very objectionable odor. Although the alkaline method is a simple process, there are several obstacles for scaling up this method, namely consumption of large amounts of alkali reagents which calls for high amounts of acid to neutralize and recover the protein, and damage and dissociation of the protein backbone (Shavandi, Silva, et al. 2017; Alahyaribeik and Ullah 2020). In alkali concentrations lower than 15%, there is a direct relationship between the keratin solubility and the alkali concentration. In the study performed by Smith et al., an alkali concentration higher than 15% increased the strength of wool fiber by ~30% when the concentration of NaOH was increased from 15% to 38%. However, cysteine a major amino acid in wool is decomposed in a high alkaline solution. Therefore, adjusting the process parameters to preserve cysteine during the protein extraction process is necessary (Vineis et al. 2019).

Ionic liquids (ILs) have been used for various applications such as biomass extraction, inorganic synthesis, and electrochemistry as ion conductive media and catalysts. Besides, due to their unique physicochemical properties, including green solvent, low vapor pressure, non-flammability, high solvation, high ion conductivity, high thermal stability, ILs are widely used as a solvent for silk, wool, cellulose, and chitin (Shavandi, Silva, et al. 2017; Shavandi et al. 2021). Wang et al. (Wang and Cao 2012) used 1-hydroxyethyl-3-methylimidazolium bis (trifluoromethanesulfonyl) as a hydrophobic ILs to extract keratin from chicken feathers. The influences of ILs, $NaHSO_3$ (reduction agent), reaction time, and temperature have been investigated on the extraction yield, which revealed that with the increase of mass ratio, keratin yield increases from ~7.5% to 17%. However, when the mass balance was 1:1, the increase in extraction yield was insignificant. Temperature is another vital factor affecting the yield of keratin extraction as the dissolution rate of feather keratin has been studied at different temperatures (70-100 GDNF). The temperature influence on yield was found in three stages: 1) an increase from 70 to 80 °C increased the yield; 2) an increase from 80-90 °C did not affect the yield, and 3) an increase from 90-100 °C decreased the yield markedly.

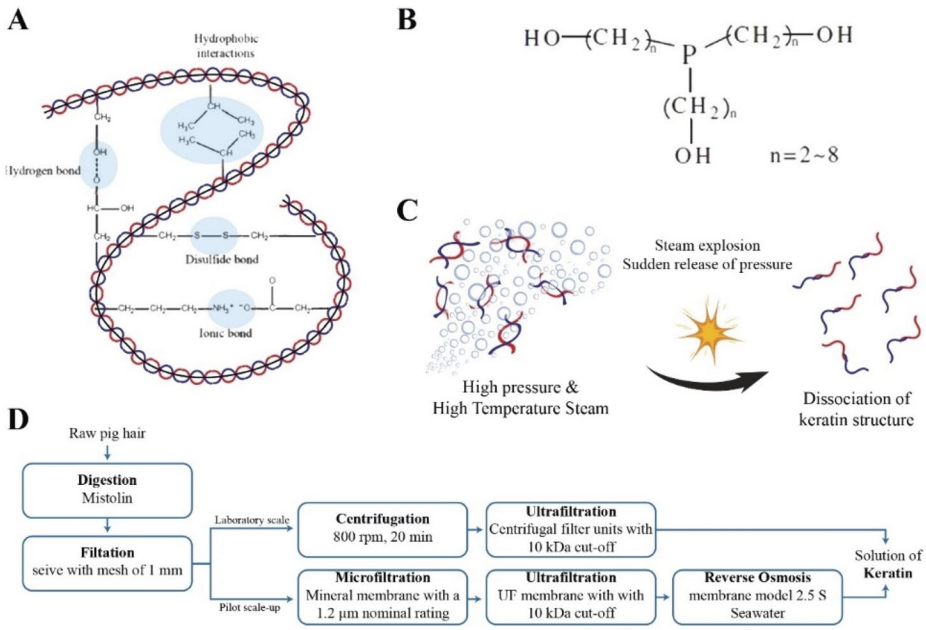

Figure 7. A) Various inter and intra-molecular chemical bonds such as hydrogen, ionic, and disulfide bonds of keratin that increase stability of keratin (Adapted from (Shavandi, Silva, et al. 2017)), B) Chemical structure of LKS-610 (Adapted from (B. Li et al. 2019)), C) Schematic of the function of steam flash explosion process for keratin extraction (Adapted from (Shavandi, Silva, et al. 2017)), D) Schematic representation of new eco-friendly keratin extraction method from pig skins developed at laboratory scale and scale-up pilot (Adapted from (Cassoni et al. 2018)).

Supercritical water and steam explosion are greener hydrolysis processes with low environmental impact and cost (Ramya, Thangam, and Madhan 2020). A steam flash explosion has been reported for keratin extraction by Zhang et al. (Zhang, Zhao, and Yang 2015). In this process, the material is initially exposed to high-temperature steam for a short time to allow the steam to penetrate the substance. After that, decompression and explosion occur in a millisecond-long reaction. The mechanical energy from thermal conversion in fast decompression results in physical tearing and dissociation of biomass (Chilakamarry et al. 2021). Figure 7c illustrates a schematic of the function of steam flash explosion for keratin extraction (Shavandi, Silva, et al. 2017). The high temperature at this method might defect the disulfide bonds in the keratin fiber. Zhang et al. (Zhang, Zhao, and Yang 2015) applied a steam flash explosion process followed by alkali treatment for keratin extraction from duck feathers. Their results showed that a combined steam flash explosion with alkali treatment could promote the dissolution of feather keratin. The effect of pressure (1.4-2.0 MPa) and the duration of applied pressure (0.5-5) have also been investigated and under the optimal extraction condition, the extraction rate and yield were 65.78% and 42.78%, respectively.

Microbial and enzymatic methods can be used to degrade and hydrolyze keratin to peptides (Falco 2018; Qiu et al. 2020). However, the exact mechanism for keratin degradation by bacteria has not been reported. One of the microbial proteases that can hydrolyze keratin is keratinases produced by certain microorganisms (Qiu et al. 2020). Keratinases have a wide range of applications, including finishing treatment of textiles, cleaning and treatment of obstruction in a sewage system, and mild and gentle removal of hair from the hide in the leather industry (Shavandi, Silva, et al. 2017; Eslahi, Dadashian, and Nejad 2013). The hydrolysis of keratin by microbial enzymes under certain processing conditions does not damage the protein backbone and preserves its functional properties (Qiu et al. 2020).

Figure 7d illustrates a new eco-friendly extraction method developed for extraction keratin at laboratory and scale-up pilot.by *Cassoni* et al. (Cassoni et al. 2018) for keratin extraction at laboratory and scale-up pilot. A commercial detergent has been used belonging to the degreaser's category capable of efficient and fast dissolution of pig hair. After removing residues by simple filtration, the obtained solution is submitted to an ultrafiltration process. Finally, a solution is obtained with protein purity of up to 70% and a yield extraction of 50%.

The source and extraction method define the potential applications of extracted keratin. Reduction, oxidation, and sulphitolysis are keratin-based denaturation extraction method that can selectively break hydrogen bonds and inter/intra disulfide bonds without damaging the keratin structure. Although these methods produce keratin with the highest molecular weight, it takes longer and utilizes a lot of chemicals, which can be toxic and pollute the environment. The usage of l-cysteine and sulphitolysis for reduction can be scaled up to industrial applications. The molecular weight of keratin extracted by eco-friendly methods such as ionic liquid, steam explosion, alkali, microwave, and superheated water depends on the process parameters. The extracted keratin has a molecular weight of lower than 10 kDa, which makes it unsuitable for structural materials. Thermal methods for keratin extraction (superheated water, steam explosion, and microwave) that destroy keratin by hot water and high pressure (without employing chemicals)

are such green methods, while their yield is low. The conversion and yield of the keratin extracted by an enzymatic process are not explicit, and it is a very high-cost process. Therefore, more research and development are needed to access cost effective and set up a green and sustainable approach to generate reproducible keratin with the same physicochemical properties based on keratin source and extraction method that can obtain keratin usable in biomedical applications.

Silk and sericin pretreatment and extraction

Amorphous sericin is extracted by a thermo-chemical process, also known as degumming (DeBari et al. 2021) which is a hydrolytic or enzymatic catalysis process of peptide bonds cleavage to remove harsh and stiff sericin (Kim, Kwon, and Kim 2016; DeBari et al. 2021). Conventional degumming processes entail extraction with boiling or hot water with soap, alkaline, organic acid solution, and synthetic detergent (Kim, Kwon, and Kim 2016). The applied degumming process influences the final fate of regenerated fibroin; various degumming reagents, advantages, and disadvantages of various degumming protocols for silk extraction are listed in Table 6.

Although Marseilles soap, which is made from olive and vegetable oil is known as a traditional hard soap, is recommended for the degumming process, it is costly and cannot compensate for the acidity of sericin hydrolysis products (Kim, Kwon, and Kim 2016). Nowadays, synthetic detergents have replaced soaps for the continuous degumming system where strong alkaline compounds are added to the degumming bath (Kim, Kwon, and Kim 2016); NaOH and Na_2CO_3 are the most used alkaline compounds for the silk degumming process. After sericin removal, the degummed fibers should be dissolved in organic or aqueous solvents to regenerate fibroin protein solutions, depending on the cocoon source (Kim, Kwon, and Kim 2016). Various solvent systems like urea (Abdullah et al. 2021), LiBr (Wang, Zhang, and Wei 2020), $CaCl_2$/ethanol/water (Sinna et al. 2021), LiSCN (Abdullah et al. 2021), and NaOH (Eom et al. 2020), have been reported. The purification of the fibroin after evaporation of the solvent is realized by dissolving it in 1,1,1,3,3,3-hexafluoro-2-propanol, and formic acid. Kundu et al. (Kundu et al. 2014) investigated four degumming methods, including urea buffer, NaCl solution, Na_2CO_3 method, and modified NaOH based extraction for fibroin isolation from silkworm species such as *Bombyx mori*/mulberry, *Antheraea mylitta*/Indian tropical tasar, *Antheraea proylei*/Temperateoak tasar, *Antheraea assamensis*/Muga, as well as *Philosamia ricini*/Eri (Figure 8a). Treatment with Na_2CO_3 in all silkworms except *B. mori* and *A. proylei* showed the highest percentage of extracted sericin. However, these methods are common for removing the sericin, releasing toxic materials (soap, acid, and alkali) into water streams, and degrading proteins into peptides with a molecular weight of 5-20 kDa are among the downsides of this method (Toprak, Anis, and Akgun 2020).

Recently, enzymatic degumming processes have drawn attention because they are more environmentally friendly, and the obtained product has improved quality and mechanical properties. Enzymatic degumming is carried out with proteolytic enzymes that are very effective in removing sericin (Shen 2019). Enzymes can hydrolyze both sericin and fibroin; however, the hydrolysis of amorphous sericin sections is easier than the high crystalline fibroins (Figure 8b). It should be noted that enzymatic degumming cannot remove sericin completely (Guo, Li, and Kaplan 2020). Table 7 summarizes some of the proteolytic enzymes that degrade silk fibroin. The enzymatic degradation starts with the hydrophilic amorphous domains, including the N-termini, C-termini, linker segments in the chains (heavy and light chains) (Shen 2019; Guo, Li, and Kaplan 2020). Using ultrasound, infrared radiation, and steam autoclave can modify sericin extraction and improve environmentally friendly and economic yield. A comparative study of ultrasonic degumming of silk sericin using citric acid (acid), Na_2CO_3 (alkaline), and papain (enzymatic) as a degumming agent showed that the ultrasonic method is more effective than the conventional heating bath (Wang, Pan, et al. 2019); lower frequency results in a greater degumming rate for all three degumming agents. Papain had the highest effect for sericin removal with a degumming rate of 22% at 60 °C under ultrasonic irradiation at 40 kHz. Negligible change in the fiber

Table 6. Advantages and disadvantages of various process and reagents used for silk degumming.

Degumming method	Degumming reagents	Advantage	Disadvantage	Ref
Soap	Marseille, sodium myristate, sodium laurate, and sodium stearate	soaps can prevent degummed fibers coagulation and improve their luster	It is possible that insoluble metal soaps be present in fibers	(Chopra and Gulrajani 1994; Biswal et al. 2022; Kim, Kweon, and Jo 2021)
Alkali	Na_2CO_3, $NaHCO_3$, Na_2HPO_4, Na_3PO_4, $Na_2[B_4O_5(OH)_4].8H_2O$	Improved productivity, low cost, and easy processing	When they are used alone, may fibers get a yellowish color	(Chopra and Gulrajani 1994; Luo et al. 2019; Rastogi and Kandasubramanian 2020; Biswal et al. 2022)
Acid	Oxalic acid, tartaric acid, lactic acid, citric acid, glacial acetic acid, and dichloroacetic acid	Fast degumming rate and needless heat	The acids may damage degummed fibers surface and structure	(Chopra and Gulrajani 1994; Gulrajanid, Sethi, and Gupta 1992; Rastogi and Kandasubramanian 2020; B. Biswal et al. 2022)
Enzyme	protease XIV, α-chymotrypsin, proteinase K, papain, matrix metalloproteinases-1, matrix metalloproteinases-2, and collagenase	Minor damage to the structure and surface of the fiber (moderate temperature and pH)	Due to the use of moderate temperature and pH, this method cannot remove all hydrophobic impurities	(Chopra and Gulrajani 1994; Rastogi and Kandasubramanian 2020; Biswal et al. 2022)

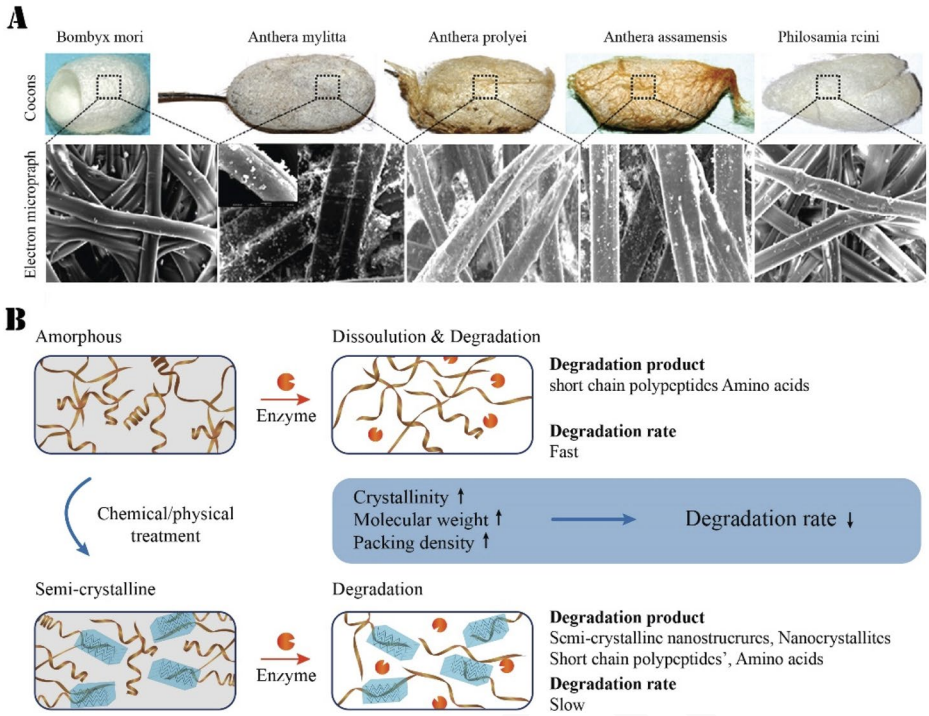

Figure 8. A) Non-woven unprocessed surface structure and electron micrographs of the fibroin-sericin combination of *Bombyx mori/mulberry, Antheraea mylitta/Indian tropical tasar, Antheraea proylei/Temperateoak tasar, Antheraea assamensis/Muga, and Philosamia ricini/Eri* (Reprinted from (Kundu et al. 2014) with permission from Elsevier), B) Schematic representation of enzymatic dissolution and degradation of amorphous sericin section and crystalline fibroin section (Adapted from (Guo, Li, and Kaplan 2020)).

structure was observed by using Fourier Transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD) when papain was used as a degumming agent (Wang, Pan, et al. 2019).

Degumming methods, either based on chemical treatments or enzymatic methods, can damage the protein structure, and break them into low molecular weight peptides and pollute the downstream flows by their residues. Moreover, purification of the final products is necessary. The hot water degumming method with a maximum recovery percentage and minimum protein damage is a reliable method that can be merged with autoclave and infrared irradiation. Although lyophilization is a common method and it has been proved that sericin extracted by this method has good biological and physical properties, it is an energy-intensive method that can damage the protein. Alternative to lyophilization, salt leaching or spray drying are more environmentally friendly and need less energy. Due to faint development and production on a small scale, sericin, and silk do not yet have international and industrial markets. To reach international markets, a sustainable method with a high yield for producing high-quality sericin and silk is necessary.

Elastin pretreatment and extraction

Insoluble elastin could be obtained after removing fats, soluble proteins, and collagen. Hot alkali treatment followed by heating at temperatures near 100 °C is ideal for achieving a purer and soluble elastin protein; however, these conditions may cause partial hydrolysis of elastin. Undesirable peptide bond cleavage occurs at a high temperature when treatment prolongs longer than 50 min (Halabi and Mecham 2018). Autoclaving, which is milder than hot alkali because the final product is less degraded. However, it has also been used for purification. However, autoclaved elastin contains additional impurities (Halabi and Mecham 2018). To minimize elastin damage, several approaches have been developed and are summarized in Table 8. The purity of elastin cannot be evaluated by using standard techniques such as

Table 7. Summary of some of the proteolytic enzymes for silk fibroin degradation (Guo, Li, and Kaplan 2020; Brown et al. 2015; Wongpinyochit, Johnston, and Seib 2018).

Enzyme	Cleavage sites	No. of cleavage sites in silk fibroin
protease XIV	Tyrosine, Phenylalanine, Tryptophan, Histidine, Lysine, Arginine	~390
α-chymotrypsin	Tyrosine, Phenylalanine, Tryptophan, Valine, Isoleucine, Leucine	~520
proteinase K	Histidine, Phenylalanine, Tryptophan, Tryptophan, Alanine, Isoleucine, Leucine, Proline, Valine, Methionine	~2200
papain	Lysine, Arginine	~40
matrix metalloproteinases-1	Glycine-Isoleucine, Glycine-Leucine	<10
matrix metalloproteinases-2	Glycine-Isoleucine, Glycine-Leucine, Glycine-Valine, Glycine-Phenylalanine, Glycine-Asparagine, Glycine-Serine	~600
collagenase	X-Glycine-Proline	~15

Table 8. Summary of various elastin isolation methods.

	Isolation method	Requirement	Advantage	Disadvantage	Ref
Harsh methods	Hot alkali	NaOH, boiling water	Easy process, low cost	Harsh extraction conditions, extensive peptide bonds cleavage	(Halabi and Mecham 2018; Gundiah, Ratcliffe, and Pruitt 2007)
	Autoclaving	Autoclave	Milder than hot alkali, less degradation of peptides	contamination, need an autoclave	(Halabi and Mecham 2018; W. Daamen et al. 2001)
Mild methods (incorporating enzyme treatment and reduction agents	Starcher method (containing 6 steps)	Na_2HPO_4, NaCl, EDTA Water, autoclave Tris buffer, $CaCL_2$, trypsin Formic acid, cyanogen bromide Tris buffer urea, α -mecaptoethanol Ethanol, acetone, water	More purified products, less damage to peptides,	Long process, higher cost	(Halabi and Mecham 2018; Starcher and Galione 1976; Daamen et al. 2005)
	Daamen method	NaCl, ethanol Chloroform, methanol, acetone, ether Formic acid, cyanogen bromide Water, tris-HCL, urea, β -mecaptoethanol NH_4HCO_3, trypsin NaCl, water			

chromatography or electrophoresis because elastin is an insoluble protein. However, chromatography technique can be used for detection of remaining contaminations after elastin purification. Instead, characteristics such as the lack of collagen (hydroxylysine and high hydroxyproline) and carbohydrates, the content of total amino acid composition and glycine, cysteine residues could be used to determine the product quality. The crosslinking amino acids liberated by acid hydrolysis, namely desmosine and isodesmosine have been used to test elastin content and purity (Ferraro, Anton, and Santé-Lhoutellier 2016). Yoseph et al. used raw hide trimming waste as a source for extracting elastin through a thermo-chemical treatment method using alkali pretreatments (Yoseph et al. 2020); the yield was ~ 90%.

Recovery

Recovery of extracted protein is a prerequisite; some recovery methods are being used, such as salting out, electrophoresis, membrane filtration, and chromatography. in the recovery stage, the focus is on separation of the proteins of interest from the solution or precipitate generated following dissolving. Spray drying to make thermally sensitive protein powder is the most popular method for protein recovery based on drying the sample water. The covalent and non-covalent bonds of proteins can be damaged by heat during the drying process by hot gas (spray drying) and influence on physicochemical properties of final products (Dehnad, Mahdi Jafari, and Afrasiabi 2016). An alternative method for drying and recovering proteins by avoiding heat damage is freeze-drying. Freeze drying is a high-performance method for drying and concentrating proteins and peptides because they are more stable in solid form. Freeze-drying increased the gelatin yield recovered from *Labeo rohita* swim bladder by NGF 13 g (per 100 g dry weight of raw material) over spray drying (Kanwate, Ballari, and Kudre 2019). Although freeze-drying and spray drying are simple, and have a high recovery rate, they raised the impurity of final protein by trapping additional large and heavy components during the drying (Cao et al. 2021).

One of the commonly applied recovery methods is the isoelectric process-isoionic point of any proteins defined by type, number, the dissociation constant of proteolytic groups. The isoelectronic method can be performed and carried out in analytical, preparative, microscale, and microfluidic channels, capillaries, and multi-compartment electrolyze (Pergande and Cologna 2017). Therefore, by re-adjusting the pH in the protein-rich solution after the solubilization step, the proteins precipitate. Thus, it could be further separated from the solution by methods such as filtration and centrifugation (Zhao et al. 2018; Malik and Saini 2019). In some case, urea and thiol compounds can be used to boost the recovery rate of less soluble and sensitive proteins (Malik and Saini 2019).

Salting out is another purification method that reduces protein solubility in the solution. Polar amino acids and charged proteins are dissolved in water due to their hydrophilic interactions. In a high ionic strength aqueous environment, the molecules with the least solubility in water precipitate at a certain ionic strength because water molecules have better interactions with ions than them. Salting-out method relies on the solubility of proteins in aqueous solution based on their ionic interaction, which depends on the type of salt, size, surface area, and charge of the protein, and the ratio of salt/protein, which type, and concentration of the salt can be varied to access optimum precipitation. The ability of some of salts (anion and cations) in interaction of water and solutes has been organized by Franz Hofmeister that the arrangement for cations is $NH_4^+ > K^+ > Na^+ > Li^+ > Mg^{2+} > Ca^{2+}$ and for anions is $F^- \geq SO_4^{2-} >$

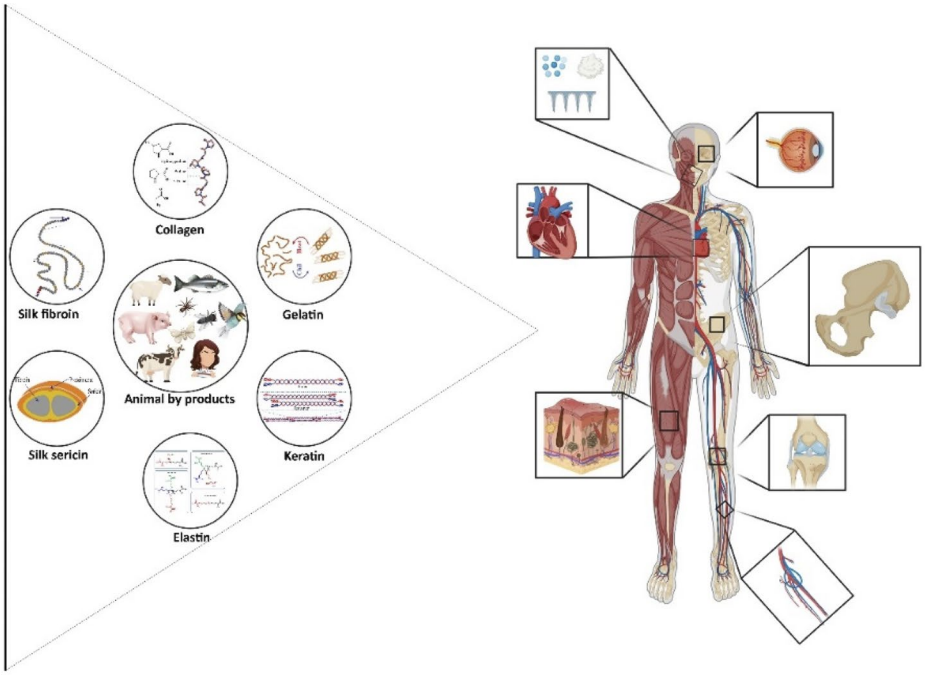

Figure 9. Application of protein-based biomaterials in tissue engineering and drug delivery.

$H_2PO_4^-$> H_3CCOO^-> Cl^-> NO_3^-> Br^-> ClO_3^-> I->ClO (Libretexts 2020). Thus, for salting in NaCl and for salting out CNTF are chosen. Although the salting out system is easy to scale up and efficient, they release a large amount of salts in down flow that must be recycled to decrease the cost and prevent of them toxic effect on environment (Tu et al. 2018). Another issue for using salting out is colored matters in the upper phase due to partial partitioning. By replacing a hydrophilic solvent with hydrophobic one, however, the recovery will be decreased. Therefore, more research is needed to find a method to maximize recovery while reducing coloring materials in salting out method (Mohammadpour 2018). Moreover, salt recovery and downstream recycling methods and approaches must be used. The isoelectronic process showed a higher yield (× 3) than salting out method for extracted collagen from bigeye tuna skins. It produced less water waste than salting-out due to the low salt concentration (Lin et al. 2019).

Ultrafiltration is a greener method for protein recovery that is based on membrane separation, in which membranes capable of retaining particles with a size of 0.001 to 0.02 microns are used in solutions for the recovery and separation of proteins (Boye and Barbana 2012). The type of the membrane, size of the pores, operating pressure, solvent pretreatment, and temperature are parameters that remarkably influence filtration (Krishnan et al. 2020; Jaramillo-Quiceno et al. 2021). The advantages of this type of filtration are the selective separation of proteins, which leads to the extraction of desired proteins by adjusting the porosity and type of the membrane. Membranes based on polymers, especially polysulfone and silicon are used to filtrate food waste. Waste streams of poultry industry containing protein pass through the polysulfone membrane with an M_W=30KDa to collect the proteins (Shahid, Srivastava, and Sillanpää 2021). It is reported that the most effective way to reduce the environmental impact and economic costs for scale-up a protein extraction from fish waste process is water recovery system by ultrafiltration and nanofiltration (Abejón et al. 2018). The process's total expenses depended on the amount of fresh water that could be decreased by adding an additional nanofiltration so that the final cost of process diminished between 25 to 49% (Abejón et al. 2018). When employing membranes for separation, two challenges must be considered: 1) effective approaches to clean the membrane to avoid of decreasing of performance (membrane fouling), 2) minimizing the nutrients concentration in the downstream to reach high quality products (Shahid, Srivastava, and Sillanpää 2021). Membrane fouling, an irreversible deposition can develop during the recovery process as a result of pore blocking and concentration polarization effect, reducing flow, efficiency, and recovery rate, and as a result increasing process costs especially on an industrial scale (Issaoui and Limousy 2019).

However, single methods like salting out, filtration, isoelectronic are very common for protein recovery; a complete protein recovery is it is challenging. Therefore, the combined methods are used for protein recovery and increased recovery rate. Further investigations are needed to increase the efficiency of current techniques or develop new large scalable technologies to cover the future need.

Purification

After recovery of the desired proteins, it is time to increase the purity and finally dry the product. Frequent washing steps, applying different solvents, adjusting pH during washing, centrifugation, and filtering effectively remove the

impurities to a large extent (Goldring 2019); however, to further increase the purity of the product and minimize batch-to-batch variation, diafiltration has been shown as a practical approach (Baldasso et al. 2022). In this method, various ultrafilters are used repeatedly while the washing process is performed between the steps. A simulation showed using ultrafiltration and diafiltration (a coupled process) may increase the whey protein yield up to 98.6% (Baldasso et al. 2022). Furthermore, it has been illustrated that by coupling ultrafiltration and diafiltration facilities purification (Opdensteinen et al. 2018). Dialysis is also another very effective way of purifying proteins in non-industrial scales, especially when it comes to removing small molecules with a semipermeable membrane. Another common approach is chromatography, and various techniques such as ion exchange, gel filtration, and reversed-phase are exploited to remove residual agents and impurities from the network of recovered proteins. Repeating the purification and recovery steps provide the product for the renaturation process of the target proteins. After the purification process, which can, in some cases, increase the purity up to 10%, the obtained proteins are dried by freeze-drying, drum drying, or spray drying to remove the remaining solvent and attain the final product . The efficiency of protein separation processes is ultimately evaluated by the measurement of several factors such as protein recovery (%), protein yield (%), and protein purity (%).

Protein-based biomaterials

Given proteins' pivotal structural and functional roles in living systems, particularly in the ECM, protein-based biomaterials have been among the most popular candidates for appliances in biomaterials and biomedical engineering. In the tissue engineering field, it is essential to fabricate a cyto/biocompatible scaffold that closely mimics the physical and chemical properties of the native ECM in the targeted tissue (Abedi, Hasanzadeh, and Tayebi 2019; Babaie et al. 2020). For instance, in cardiac muscle tissue, electrical conductivity is of great importance, while in musculoskeletal tissues such as bone and cartilage, biomechanical properties come first (Qin, Hu, and Li et al. 2020). Protein-based biomaterials have shown promising results (Asadpour et al. 2020). In addition to their biocompatibility and biodegradability, protein-based biomaterials present great variation in composition, structure, and shape that can meet the requirements in a wide range of tissue engineering applications. Some of the recent biomedical applications of collagen, gelatin, keratin, silk fibroin, and elastin-based biomaterials are deliberated in the following sections (Table 9).

Collagen

Collagen is widely used in tissue engineering, especially in scaffold fabrication (Silva et al. 2014; Lo and Fauzi 2021) as collagen-based materials have shown great potential for skin tissue regeneration because it composes the main biomolecules present in the skin. Although different types of collagens can be produced from animal by-products, collagen type I is the most abundant collagen, as seen in Tables 4 and 9. Collagen type I, on the other hand, account for 90% of the total collagen in the human body. The content and composition of amino acids in collagen structure explain its properties, especially hydroxyproline, responsible for temperature stability, rigidity, and denaturation temperature (Oosterlaken, Vena, and de With 2021). The hydrogen bonds between the hydroxyproline and hydroxylysine via their hydroxyl groups increase the collagen thermal stability (Babu and Ganesh 2001; Li et al. 2021). Therefore, the expected properties can determine the collagen source and extraction method. The potential of type I collagen derived from tilapia skin was investigated by *Li* et al. (Li et al. 2018) as a biomaterial for skin tissue engineering. According to the histocompatibility and tissue adaptation examinations, it was revealed that after 15 days of in vivo implantation, the microfibrous collagen matrix scaffold of tilapia skin was degraded into tiny fragments. After 20 days of implantation, the scaffolds were absorbed entirely and degraded. In addition to marine animal-derived collagen, mammalian-derived collagen is widely utilized as biomaterials in tissue regeneration applications. *Fauzi* et al. have developed thin films (aligned collagen film and random collagen film) from ovine tendon collagen for applications in tissue engineering (Fauzi et al. 2016). Human dermal fibroblasts exhibited higher attachment and growth rates as indicated by live and dead cell staining and the percentage of cell attachment on ovine tendon collagen films compared to a polystyrene surface.

Despite these exciting results, low mechanical strength and rapid in vivo degradation limit collagen applications (Zhang et al. 2020). Therefore, to improve its properties, several methods have been recently reported, such as using suitable cross-linkers and synthesis of hybrid hydrogels based on blending collagen with other polymers and nanoparticles (NPs) (Nikolova and Chavali 2019; Yang et al. 2018; Kolanthai et al. 2018; Türk et al. 2018). For example, *Sun* et al. (Sun et al. 2020) fabricated sponge-like scaffolds from Nile tilapia skin by lyophilization using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide in the presence of *N*-hydroxysuccinimide (EDC/NHS) as the crosslinking agents; macro morphology of non-cross-linked and EDC/NHS cross-linked collagen sponges are shown in Figure 10a. The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay results showed that EDC/NHS cross-linking does not negatively affect fibroblast cell viability and proliferation. The EDC/NHS cross-linked collagen sponge sample exhibited the best blood clotting ability with a bleeding time of 137 s, blood loss of 0.95 g, and hemostatic efficiency in vivo (rat femoral artery hemorrhage model) (Figure 10a). In another study, Govindheraj et al. used extracted collagen from Eel fish skin to design a 3 D scaffold by blending collagen with alginate (Govindharaj, Kiran Roopavath, and Narayan Rath 2019). The ensuing material was used for 3 D bioprinting Human umbilical derived mesenchymal stem cells (Figure 10b). After seven days of culture, the metabolic activity was significantly improved ($p < 0.01$), and similarly live/dead staining revealed that the number of live cells was

Table 9. Summary of biomaterials applications by protein type, recent data from the literature. Q11

Composition	Extraction method	Waste source	Biomaterial form	Application	Ref
Collagen	ASC and PSC	Nile tilapia skin	Sponge	As hemostatic dressings	(Sun et al. 2020)
	ASC and PSC	giant croaker (*Nibea japonica*) swim bladders	Sponge	Antioxidant properties of giant croaker (*Nibea japonica*) swim bladders collagen and wound healing evaluation	(Chen et al. 2019)
	–	Porcine	Sponge	Curcumin loaded chitosan NPs incorporated into collagen/ alginate scaffolds for diabetic wound healing	(Karri et al. 2016)
	PSC	Bovine tendon	Sponge	Silver NPs loaded within collagen/chitosan scaffolds to promote wound healing	(You et al. 2017)
	–	Fish	Nanofibers	Collagen nanofiber containing silver nanoparticles for improved wound healing	(Rath et al. 2016)
	PSC	Bovine tendon	Hydrogel	Bacterial cellulose/collagen hydrogel for wound healing	(Moraes et al. 2016)
	ASC	Tilapia skin	Sponge	Electrospun tilapia collagen nanofibers accelerate wound healing	(Zhou et al. 2016)
	ASC	Rat tail tendon	Nanoparticles	Collagen/ ZnO scaffolds for wound healing applications	(Vedhanayagam, Nair, and Sreeram 2018)
	ASC	Shark skin (Prionace glauca)	Sponge	Marine collagen/apatite composite scaffolds to hard tissue applications	(Diogo et al. 2018)
	ASC and PSC	Blue shark skin		Blue shark skin collagen as a biochemical for bone tissue engineering	(Elango et al. 2018)
	ASC	Jellyfishes	Sponge	Keratin/jellyfish collagen/ eggshell-derived hydroxyapatite osteoinductive biocomposite scaffolds for bone tissue engineering	(Arslan et al. 2017)
	purchased	Porcine	Composite scaffold	Dexamethasone-loaded biphasic calcium phosphate nanoparticles/collagen porous composite scaffolds for bone tissue engineering	(Ying Chen, Kawazoe, and Chen 2018)
	PSC modified	Rat tail tendon	Hydrogel	The hydrogel containing naringin to sciatic nerve regeneration	(Samadian et al. 2019)
	Acetic acid and HCL	Rat tail tendon	Sponge	olibanum-collagen-gelatin scaffolds for efficient neural tissue regeneration	(Ghorbani et al. 2020)
	Modified ASC (autoclaved 0.6% acetic acid in phosphate-buffered saline (PBS) at a final concentration of 20 mg/mL)	Rat tail tendon	Hydrogel	The hydrogel containing chitosan nanoparticle loaded by insulin for sciatic nerve regeneration	(Ai et al. 2019)
	purchased	Rat tail and chicken sternal	Hydrogel	Collagen type I and II blended hydrogels for articular cartilage tissue engineering	(Vázquez-Portalatín et al. 2016)
	ASC	Eel fish skin	3D printing	Biomaterial for tissue engineering	(Govindharaj, Kiran Roopavath, and Narayan Rath 2019)
	ASC	Tilapia skin	Microfiber collagen matrix	Potential application in biomedical scaffold material for tissue engineering	(Li et al. 2018)
	ASC	Fish scales	Sponge	Chitosan/fish scale collagen/ lovastatin nanocomposites for drug delivery	(Tran et al. 2020)
	Supercritical fluids technology	Atlantic cod (*Gadus morhua*) skins	–	The extracted collagen demonstrated nontoxicity; so it can be used for health care applications	(Sousa et al. 2020)
Keratin	Reduction	Human hair	Sponge	Human hair keratin for the regeneration of peripheral nerves	(Gao, Zhang, et al. 2019)
	Purchased	Human hair	Nanoparticles	Two recombinant trichocyte keratins, including human type I hair keratin 37 and human type II hair keratin 81 to accelerate dermal wound healing	(Gao, Li, et al. 2019)

(Continued)

Table 9. (Continued).

Composition	Extraction method	Waste source	Biomaterial form	Application	Ref
	Reduction	Human hair	Membrane	Photo-crosslinked keratin/chitosan membranes as potential wound dressing materials	(Lin et al. 2018)
	Reduction (Shindai solution)	Human hair	Hydrogel	Carboxymethyl cellulose/keratin hydrogel with controlled clindamycin release as an antibacterial wound dressing	(Sadeghi et al. 2020)
	Reduction	Human hair	Nanofibrous	Electrospun polyurethane/keratin/AgNP biocomposite mats as an antibacterial wound dressing	(Wang et al. 2016)
	Oxidized	Human hair	3D printing	3 D printed keratin-based hydrogel for biomedical application	(Placone et al. 2017)
	Reduction	Wool	Nanofibers	keratin/polycaprolactone nanofiber membranes for cell culture	(Wu et al. 2018)
	Reduction (Shandai solution)	Goat hoof	Film	Keratin/gelatin/sodium alginate base biofilm for tissue engineering application	(Kumar, Anandhavelu, and Swathy 2019)
	Reduction	Hair	Hydrogel	Keratin/chitosan hydrogels for use in tissue engineering	(Lu et al. 2020)
	Alkali and reduction	Red sheep's hair		Valuable material for biomedical applications.	(Ramya, Thangam, and Madhan 2020)
	Reduction	Feather, wool, hair	Self-assemble hydrogel	Feather, wool, and hair keratin hydrogel for biomedical applications	(Esparza et al. 2018)
	Reduction	Wool	Nanofibrous	Keratin-polybutylene succinate nanofibrous mats for drug delivery and cells culture	(Guidotti et al. 2020)
	Reduction	Human hair	Nanoparticles	Doxorubicin loaded keratin nanoparticles for drug delivery	(Li et al. 2017)
	Reduction (Sulphitolysis)	Merino wool	Film	Keratin-hydrotalcite hybrid films for drug delivery applications	(Posati et al. 2018)
	Reduction	Human hair	Nanoparticles	quercetin loaded stable human hair keratin nanoparticles intended for anticancer drug delivery	(Kunjiappan et al. 2018)
	Reduction	Human hair	sponge	keratin/jellyfish collagen/eggshell-derived hydroxyapatite osteoinductive biocomposite scaffolds for bone tissue engineering	(Arslan et al. 2017)
	Enzymatic	Wool	–	The extracted keratin showed good antioxidant activity and promoted the growth of cells	(Su et al. 2020)
Silk fibroin	Hot water and Na_2CO_3	B. mori	Film	silk fibroin/paramylon blend films for chronic wound healing	(Arthe, Arivuoli, and Ravi 2020)
	Hot water and Na_2CO_3	Cocoon	Nanofibers	Manuka honey/silk fibroin fibrous matrices as a potential wound dressing	(Yang et al. 2017)
	Hot water and Na_2CO_3	B. mori	Sponge	Chitin/silk fibroin/TiO_2 bio-nanocomposite as a biocompatible wound dressing bandage	(Mehrabani, Karimian, Rakhshaei, et al. 2018)
	Hot water and Na_2CO_3	B. mori	Sponge	Silk fibroin/chitin/silver nanoparticles 3 D scaffolds as a bandage for antimicrobial wound dressing	(Mehrabani, Karimian, Mehramouz, et al. 2018)
	Hot water and Na_2CO_3	Spring silkworm	3D printing	Mesoporous bioactive glass/silk fibroin composite scaffolds for bone tissue engineering	(Du et al. 2019)
	Hot water and Na_2CO_3	B. mori	Nanofibrous	Electrospun poly(3-hydroxybutyrate-co-3-hydroxyhexanoate)/silk fibroin nanofibers as a scaffold for bone tissue engineering	(Ang et al. 2020)
	Hot water and Na_2CO_3	B. mori	Nanocomposite	Gold nanorods reinforced silk fibroin nanocomposite for peripheral nerve tissue engineering applications	(Afjeh-Dana et al. 2019)
	Hot water and Na_2CO_3	B. mori	Sponge	Silk fibroin/hyaluronic acid as a nerve conduit	(Yoseph et al. 2020)

(Continued)

Table 9. (Continued).

Composition	Extraction method	Waste source	Biomaterial form	Application	Ref
	Hot water and Na_2CO_3	Cocoon silkworm	Hydrogel	A silk fibroin/decellularized extract of Wharton's jelly hydrogel intended for cartilage tissue engineering	(Basiri et al. 2019)
	Hot water and Na_2CO_3	B. mori and P. ricini	3 D printing	Cross-linker-free silk–gelatin bioink for cartilage tissue engineering.	(Singh, Bandyopadhyay, and Mandal 2019)
	Hot water and Na_2CO_3	B. mori	Sponge	Silk fibroin/collagen/hyaluronic acid scaffold incorporating pilose antler polypeptides microspheres for cartilage tissue engineering	(Jianhua Wang, Sun, et al. 2019)
	Hot water and Na_2CO_3	Tussah	Film	Nonmulberry silk film for potential tissue engineering applications	(Zhang et al. 2019)
	Hot water and Na_2CO_3	Silkworm cocoon	Nanofibrous	Electrospun polyurethane/silk fibroin hybrid nanofibers as potential scaffolds for soft and hard tissue engineering	(Dehghan-Manshadi et al. 2019)
	Hot water, sodium lauryl sulfate and Na_2CO_3	B. mori	Microparticles	Control drug release behavior of polyurethane filament and the effect of silk fibroin microparticles on it.	(Zhuang et al. 2019)
	Hot water	B. mori	Film	Silk fibroin films for potential applications in controlled release	(Huang et al. 2017)
Gelatin	Ultrasonic-assisted water	Fish biowaste	Fibers	Gelatin coated phosphate-glass fibers for wound-healing application	(Sghayyar et al. 2020)
	Obtained	Bovine	Hydrogel	Cellulose nanocrystals/ gelatin/ hyaluronic acid composite hydrogel as a wound dressing	(Yin, Lin, and Zhan 2019)
	Water extraction modified with 0.05 M phosphoric acid	Unicorn Leatherjackets (*Aluterus monoceros*) skin	Sponge	Gelatin from fish skin reinforced with chitosan for bone tissue engineering	(Saah, Oungbho, and Benjakul 2017)
	Purchased	Porcine skin	Nanofibers	Silk fibroin/gelatin nanofibrous scaffolds crosslinked with glutaraldehyde vapor for tissue engineering	(Mohammadzadehmoghadam and Dong 2019)
	Purchased	Porcine skin	Hydrogel	Gelatin hydrogels for potential applications in nerve regeneration with control the fate of human umbilical cord mesenchymal stem cells	(Li et al. 2020)
	Purchased	Porcine skin	Nanofibrous	Nanofibers of modified gelatin-tyrosine in cartilage tissue engineering	(Agheb et al. 2017)
	Purchased	Bovine	3D printing	Cross-linker-free silk–gelatin bioink for cartilage tissue engineering.	(Singh, Bandyopadhyay, and Mandal 2019)
	Heating	Fish scale	Sponge	Engineered fish scale gelatin for tissue engineering. The extracted fish collagen was subjected to pressure heating for 4–6 h at >70 °C.	(Manikandan et al. 2018)
Elastin	Purchased	Bovine neck ligament	Hydrogel	Elastin and alginate hydrogel for tissue engineering applications	(Silva et al. 2018)
	Purchased	Bovine neck	Hydrogel	Hyaluronic acid and α-elastin based hydrogel for 3 D culture of vascular endothelial cells	(Fiorica et al. 2018)
	Purchased	Porcine skin	Hydrogel	Cross-linked elastin in gelatin/ PEG hydrogels for wound healing	(Cao, Lee, et al. 2020)
	Obtained	Bovine neck	Nanofibers	Nanofiber scaffold constructed from tyrosinase-treated fibroin and elastin for biomedical applications.	(Hong et al. 2016)

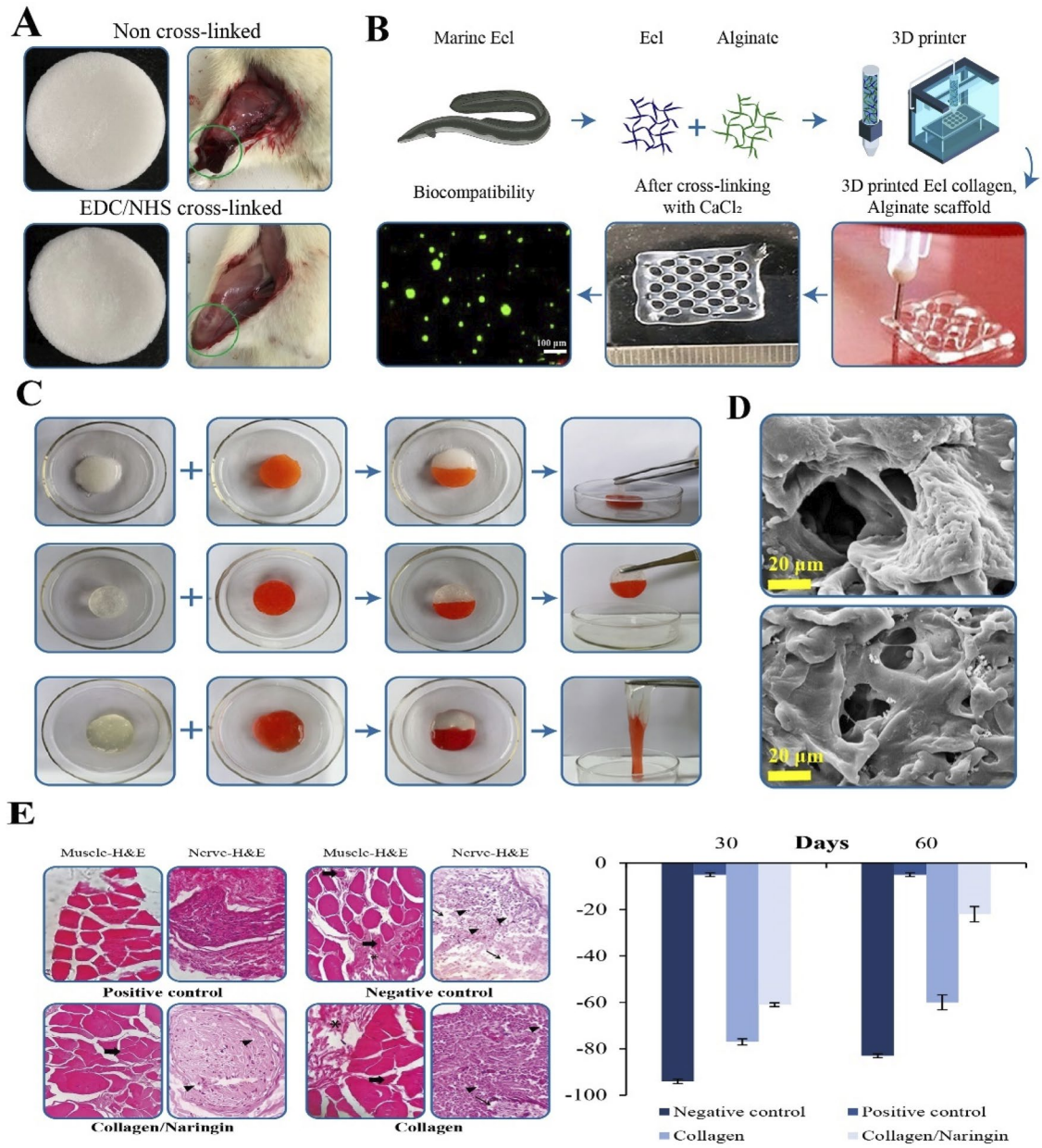

Figure 10. A) Macro morphology images of non-cross-linked and cross-linked with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide in the presence of *N*-hydroxysuccinimide (EDC/NHS) collagen sponges (Sun et al. 2020), Representation of femoral artery hemorrhage model after hemostasis and using non-cross-linked and cross-linked with -ethyl-3-(3-dimethylaminopropyl) carbodiimide in the presence of *N*-hydroxysuccinimide (EDC/NHS) collagen sponges to control bleeding (Reprinted from (Sun et al. 2020) with permission from Elsevier), B) Fabrication a 3 D printed scaffold based on extracted collagen from Eel fish skin and its biocompatibility (Adopted from (Govindharaj, Kiran Roopavath, and Narayan Rath 2019) with permission from Elsevier), C) Macroscopic images of the self-healing ability of collagen, collagen-guar gum (CGG), and collagen/collagen-guar gum with 1/1, 2/1, and 4/1 ratios hydrogel (Reprinted from (C. Ding et al. 2020) with permission from Wiley), D) the SEM micrograph images of olibanum/rat tail derived collagen/gelatin scaffolds after 3 days cultured with bone marrow stromal cells (BMSCs) (Reprinted from (Ghorbani et al. 2020) with permission from Wiley) E)The results of the hematoxylineosin staining (H&E) of the sciatic nerve, and gastrocnemius muscle after 8 weeks of surgery. Magnification for muscle: ×400, the magnification of nerve:×200 (left), sciatic functional index results of positive control, negative control, collagen and collagen/naringin scaffolds at 30 and 60 days after implantation (right) (Reprinted and adopted from (Samadian et al. 2019) with permission from Springer).

increased after seven days. In another interesting work, a self-healing collagen-based hydrogel has been developed based on dynamic network chemistry by *Ding* et al., that consists of dynamic imine linkages between dialdehyde guar gum and NH_2 collagen (Ding et al. 2020) and diol-borate ester bonds between borax and guar gum. The results of this study revealed that the denaturation temperature of native collagen hydrogel increased from 40.2 °C to 52.8 °C after cross-linking, indicating an improvement of collagen thermal stability via modification by dialdehyde-modified guar gum due to the formation of dynamic imide bonds which also paved the way for self-healing ability of the collagen-based hydrogel (Figure 10c)

Various composites of collagen have been used to construct scaffolds for neural tissue engineering. For instance, 3 D shape scaffolds based on collagen extracted from rat tail followed by olibanum and gelatin for efficient neural tissue regeneration were fabricated by *Gorbani* et al. (Ghorbani et al. 2020). The scanning electron microscope images of scaffolds after three days of culture with bone marrow stromal cells (BMSCs) showed that these composite scaffolds supported cell attachment and ingrowth (Figure 10d). In another work, *Samadian* et al. fabricated and characterized a type I collagen and naringin scaffold for peripheral nerve damage treatment (Samadian et al. 2019). The results of their in vitro study showed that the proliferation of Schwann cells on the collagen/naringin hydrogel scaffold was higher than the control group (tissue culture plate). The in vivo study of the same system after 60 days of implantation implied that the functional sciatic index significantly increased when the collagen/naringin hydrogel system was compared to the negative control Figure 10e. The same group prepared rat tail tendon collagen hydrogel containing chitosan NPs loaded with insulin for sciatic nerve regeneration. Histological assessment revealed remarkable improvements in myelin sheath regeneration where the scaffold treated groups had more resemblance to the normal sciatic nerve (Ai et al. 2019).

Research on musculoskeletal tissue engineering has also significantly benefited from collagen-based scaffolds. The ECM produced by chondrocytes mainly comprises collagen type II (90-95%), a promising scaffold material for articular cartilage. Vazquez-Portalatin et al. blended collagen type I, extracted from rat tail, with lyophilized chicken sternal collagen type II and characterized the cartilage tissue regeneration potential of the scaffold (Vázquez-Portalatín et al. 2016). They claimed the sample with a 3:1 collagen type I to collagen type II ratio has the potential to be used for cartilage tissue engineering.

Collagen has also investigated by several researchers for drug delivery purpose. For example, Zhang et al. fabricated two different nanofibrous drug delivery systems using collagen (Zhang et al. 2016). The blend and coaxial electrospun nanofibers of *Rana chensinensis* skin collagen (RCSC)/Poly (l-lactide) (PLLA) containing 5 wt% vancomycin (VCM) have been evaluated for their local and temporal drug delivery properties. While the amount of loaded drug was almost entirely released after 48 h from both nanofibers, the cumulative release from the blend sample was 97% and from the coaxial sample was 80%, two different nanofibrous systems showed differing release behaviors for VCM.

Gelatin

Gelatin is a mixture of polypeptides derived from collagen by the partial hydrolysis of the protein backbone. Gelatin possesses many desirable characteristics for tissue engineering, including biodegradability, biocompatibility, and adaptability endowing gelatin with various applications from wound healing to tissue regeneration (Sghayyar et al. 2020; Rubio-Valle et al. 2021; Askari et al. 2021; Fonseca et al. 2019). Like collagen, gelatin suffers from weak mechanical strength and rapid dissolution in an aqueous medium. Hence, many attempts have been made to strengthen the gelatin-based scaffolds and improve their hydrolysis resistance (Rajabi et al. 2021; Sheikhi et al. 2021; Zhang, Qu, et al. 2021). Sghayyar et al. investigated the wound healing potential bioresorbable phosphate-based glass fibers coated by gelatin (Sghayyar et al. 2020) extracted from the tilapia scale (Figure 11a). The cross-linked gelatin hydrogels by glutaraldehyde revealed accelerated in vitro artificial wound closure in the scratch test with 28.5% more closure than the untreated wound within 24 h (Figure 11a). Li et al. (Li et al. 2020) fabricated a new injectable dual-enzymatically cross-linked hydrogel using porcine skin-derived gelatin to investigate its potential in nerve regeneration. The in vitro and in vivo assays claimed that their injectable gelatin hydrogel holds enormous potentials in nerve regeneration and nervous disorders therapy.

In another study, a bone scaffold based on chitosan and sandfish skin gelatin extracted from unicorn leatherjackets (*Aluterus monoceros*) exhibited biocompatibility without any adverse effect after 24 h of the cells culture on all samples, and higher cells adhesion was reported on the fish gelatin containing scaffold compared to pure chitosan scaffold (Saah, Oungbho, and Benjakul 2017). *Ashwin* et al. (Ashwin et al. 2020) used different concentrations of mucic acid in combination with gelatin to coat 3 D polylactic acid (PLA) scaffolds and enhance their osteogenic potential. The mRNA expression of ALP, type I collagen (Col-1), and osteocalcin (OCN) was significantly increased in cells-seeded PLA/gelatin/mucic acid scaffolds compared to cells-seeded PLA/gelatin scaffolds. Due to its several bioactive motifs (RGD, which stands for glycine, l-arginine, and l-aspartic acid peptides), gelatin induces cell adhesion on the surface and supports their growth and proliferation (Agheb et al. 2017; Ahammed et al. 2021; J. Liu, Zhang, et al. 2021).

In addition to the several crosslinking methods for resolving the easy dissolution of gelatin, surface modification is another strategy to modify its chemical, mechanical, and biological properties. Agheb et al. used tyrosine-protein and 1,2,3-triazole ring to functionalize gelatin extracted from porcine skin and chemical cross-linkers such as glutaraldehyde and EDC/NHS to fabricate electrospun nanofibrous scaffolds for cartilage tissue engineering (Agheb et al. 2017). The mechanical properties of modified gelatin nanofibers improved by 10-20 folds in terms of Young's modulus. The modified gelatin nanofibrous did not induce any cytotoxic effect on chondrocyte cells, and gelatin scaffolds cross-linked with EDC/NHS resulted in enhanced cell proliferation when compared with the control group (Agheb et al. 2017). Singh et al. developed a cross-linker-free bioink for cartilage regeneration with optimal rheology (Singh, Bandyopadhyay, and Mandal 2019). To this end, they utilized silk fibroin (extracted from *B. mori* and *P. ricini*) and blended it with bovine gelatin. They asserted that these two naturally-derived proteins interacted through physical crosslinking and entanglement (Figure 11b). The hydrogel showed a sol-gel transition (G'>G") in the temperature ranges of 4-25 °C and 35-45 °C while exhibiting a sol behavior at 25-35 °C, which paves the way for 3 D printing of the bioink at this

temperature range considering its low viscosity. Better still, since the rheological properties of the bioink turn into solid dominant area at higher and lower temperatures, the ink could preserve its shape and serve as a good candidate for 3 D bioprinting of hydrogels in cartilage tissue engineering. Figure 11b depicts the images of Calcein AM-stained, DAPI-labelled bright blue cells, and hematoxylin-eosin (H&E)-stained cell-laden 3 D bioprinting networks.

Ahmad et al. fabricated gelatin NPs coated with Eugragit s-100 for targeted oral delivery of 5-amino salicylic acid (5-ASA) in ulcerative colitis (Figure 12a (top))(Ahmad et al. 2021). The release profile was studied in a period of 90 h and at two acidic (2.0 and 4.5) and neutral pH. The results revealed that only 1.3% of the drug was released at pH 2.0 (which represented the gastric acidic environment), 7.5% of the drug was released at pH 4.5 (representing the proximal intestine environment), and thus, most of the loaded drug remained for the pH 7.4 (which represents the colon environment). Over four days, a sustained release was observed under this condition (Figure 12a (bottom, right)). Thus, few studies on protein-based micro/nanoparticles for drug delivery systems indicate the great potential of such platforms to be adopted for specific target delivery purposes. Ramadoss et al. prepared 3 D gelatin/keratin and gelatin/silk composites with highly interconnected pores by freeze-drying technique as a potential candidate for sustained drug release (Ramadoss et al. 2017). Gelatin/keratin scaffolds exhibited rather sustained-release compared to the gelatin/silk scaffolds, and the observation was attributable to more hydrophobicity of keratin than gelatin.

Gelatin methacryloyl (GelMA) is a gelatin-based compound that has been validated for biomedical application (Shie et al. 2020). GelMA has been prepared through the reaction of gelatin with methacrylic anhydride, and via alteration of feed ratio (gelatin/methacrylic anhydride), the degree of substitution and mathacryloylation can be adjusted that are the main influential factors on ultimate properties of GelMA (Shie et al. 2020; Rastin et al. 2020). GelMA can be used as a good candidate for tissue engineering, drug delivery, and 3 D printing because it displays biocompatibility, enzymatic cleavage, cell adhesion, and tailorable mechanical properties (Rastin et al. 2020; Shie et al. 2020; C. Kim, Young, et al. 2020). GelMA hydrogel samples have been prepared with high and lowly substituted versions, and then their protein structure, mechanical properties, degradation, and cell viability have been studied (Zhu et al. 2019). Lue et al. have investigated a gelatin methacrylate (GelMA) MNs patch for sustained delivery of doxorubicin (Luo et al. 2019). To fabricate MNs, doxorubicin was mixed with GelMA, cast into a micro-mold, and crosslinked using UV (Figure 12b (top)). GelMA MNs could successfully penetrate through and bypass the mouse SC due to their high stiffness (Figure 12b (bottom)). GelMA MNs exhibited controllable mechanical properties, degradation, and drug release rate via tunning the crosslinking time.

Since gelatin is hydrolyzed from collagen, it is affected by all parameters that affect collagen properties. Hence, gelatin quality is determined by factors such as raw materials, tissue type, animal age, collagen extraction,

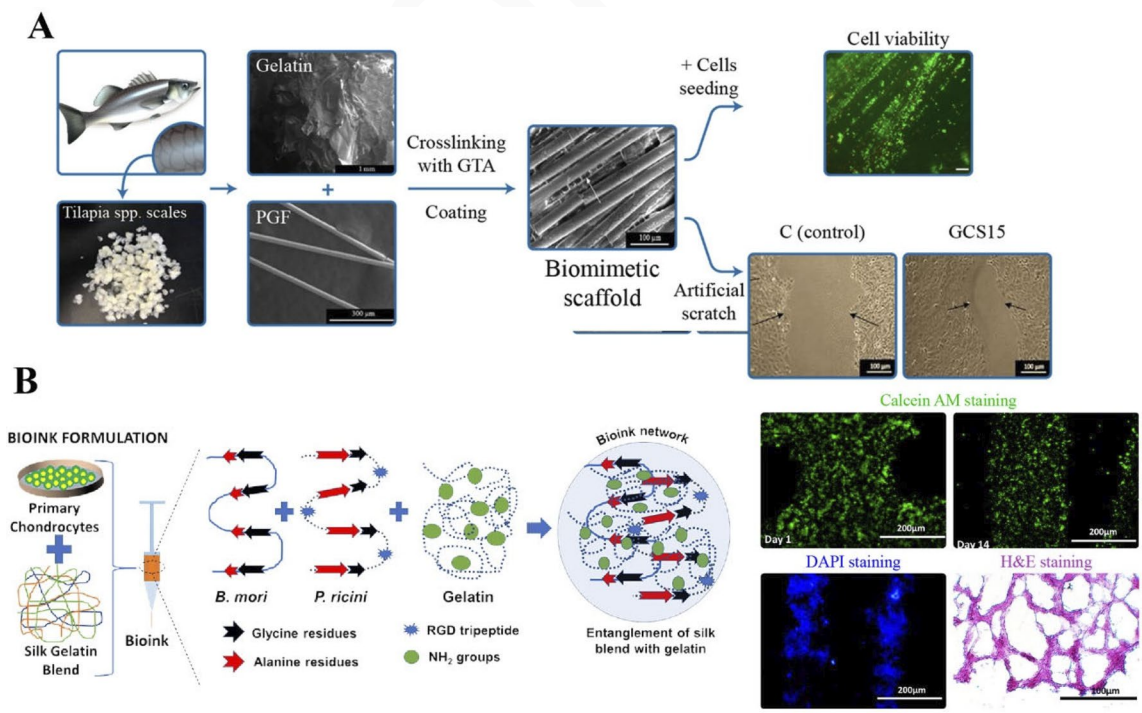

Figure 11. A) Fabrication of the hydrogel based on bioresorbable phosphate-based glass fibers that was coated with gelatin extracted from tilapia scale for potential wound healing applications and images of wound scratch assay after 24 h (Reprinted and adopted from (Sghayyar et al. 2020) with permission from Elsevier), B) Schematic representation of bioink formulation and entanglement and interaction of silk fibroin extracted from *B. mori, P. ricini*, and bovine gelatin (left), and the images of Calcein AM-stained, DAPI-labelled bright blue cells, and hematoxylin-eosin (H&E)-stained of 3 D bioprinting network based on silk fibroin extracted from *B. mori, P. ricini*, and bovine gelatin (right) (Reprinted from (Singh, Bandyopadhyay, and Mandal 2019) with permission from ASC publications.

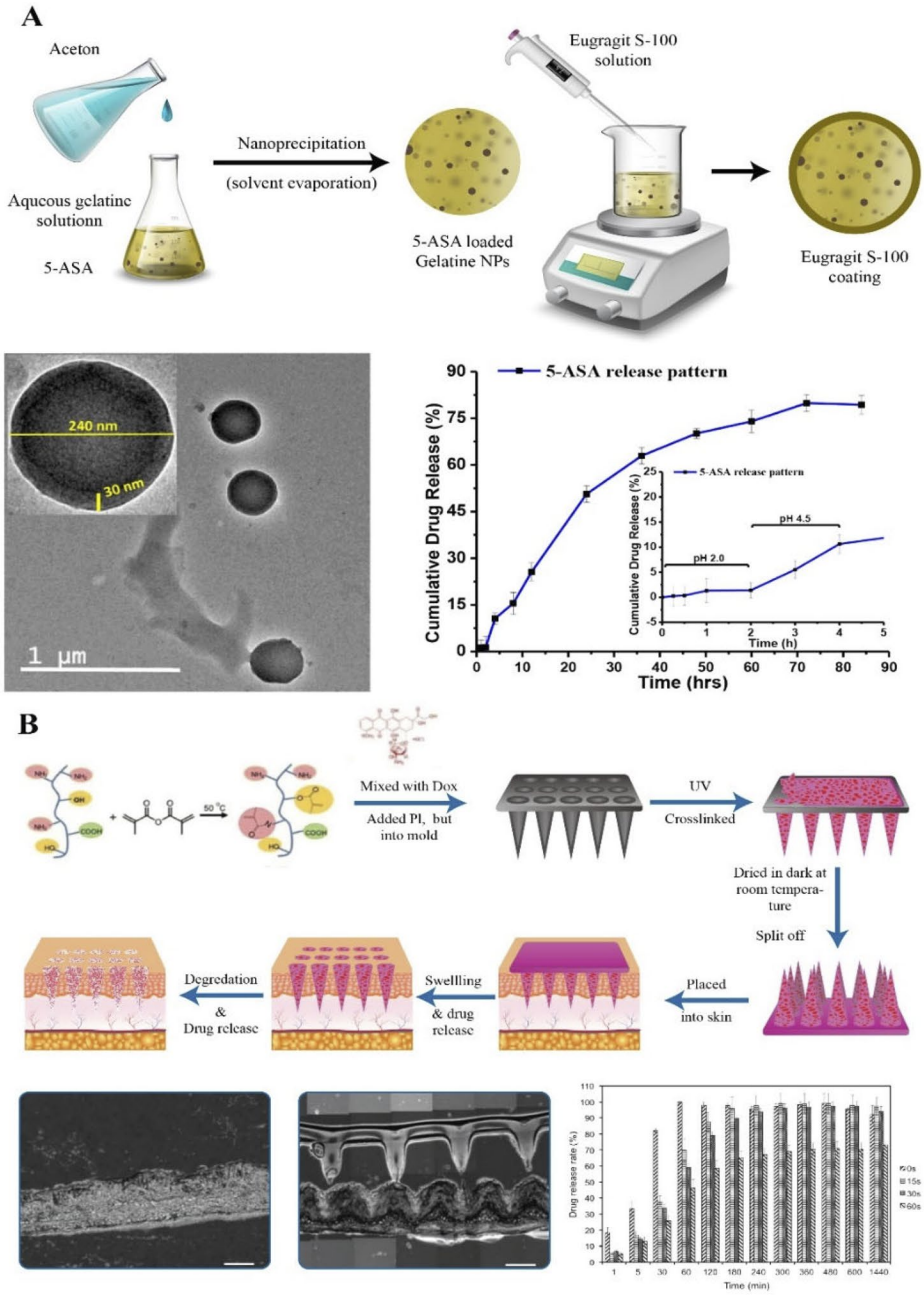

Figure 12. A) Schematic representation of the synthesis of gelatin loaded 5-ASA NPs coated with Eugragit s-100 preparation process (top), TEM photograph of gelatin loaded 5-ASA NPs coated with Eugragit s-100 (bottom, left), and 5-ASA release profile under simulated physiological condition (bottom, right) (Reprinted from (A. Ahmad et al. 2021) with permission from Elsevier), B) Schematic representation of gelatin methacrylate (GelMA) MNs patch preparation and their release mechanism (top). Microscopy images of mouse skin, before and after MNs penetration (bottom, left), and Doxorubicin (DOX) release from the fabricated MNs under different crosslinking duration (bottom, right) (Reprinted from (Luo et al. 2019) with permission from Wiley.

purification method, and hydrolysis method. For example, high temperature extraction decreases the physical properties of gelatin and its capacity to produce gel. It is not necessary to use pure collagen in skin tissue engineering or cartridge with good mechanical characteristics. By combining gelatin with high mechanical polymers, gelatin has been used in hard tissue engineering, such as bone, to improve cell attachment, proliferation, and differentiation. However, gelatin is being used in different biomedical applications, regarding target tissue should be modified via crosslinking, blending, replacement functional groups, etc.

Keratin

Many researchers have studied the applications of keratin derived from animal by-products in tissue engineering and drug delivery (Ramya, Thangam, and Madhan 2020; Gao, Zhang, et al. 2019; Gao, Li, et al. 2019; Lin et al. 2018; Sadeghi et al. 2020; Wang et al. 2016; Placone et al. 2017) and in recent years, keratin's intrinsic cell attachment and proliferative effects, biocompatibility, biodegradability, and natural abundance have attracted considerable attention for the wound healing process (Wang et al. 2017). Ramya et al. evaluated the extraction yield, keratin content, and process

cost of six different chemicals for extracting keratin from red sheep's hair (Ramya, Thangam, and Madhan 2020). Keratin enhances collagen deposition, keratinocyte migration, and fibroblast adhesion through binding to the adaptor protein in wounded stratified epithelia because of the abundance of peptide sequences of Leucine – Aspartic acid – Valine and Arginine – Glycine – Aspartic acid (Gao, Li, et al. 2019). Gao et al. fabricated NPs from human hair keratin to accelerate dermal wound healing (Gao, Li, et al. 2019). Using a bacterial expression system, they expressed two recombinant trichocyte keratins, including type I hair 37 and human type II hair keratin 81. In the live/dead viability/cytotoxicity assay, it has been shown that with increasing keratin NPs concentration from 0.25 to 1.00 $mg.ml^{-1}$, the percentages of viable cells increased (Figure 13c (right)). Wounds treated with both fabricated NPs closed faster than the control group after seven days, as demonstrated in Figure 11c (left). Keratin-based scaffolds have also shown promise in the treatment of peripheral nerve damage. Gao et al. showed that keratin extracted from human hair promotes the regeneration of peripheral nerves in a rat sciatic nerve model (Gao, Zhang, et al. 2019). The proliferation of rat Schwann cell strain significantly increased on day 5 ($P < 0.05$) and 7 ($P < 0.01$) in the keratin group compared with the control group. Moreover, the mRNA levels of the Glial cell line-derived neurotrophic factor (×), nerve growth factor (≅), and ciliary neurotrophic factor (×) were much higher in the keratin group on the first day. Although the levels of GDNF, NGF, and CNTF remained higher in the keratin group throughout the experiment, the secretion of neurotrophic factors decreased gradually. The schematics and photographs of the surgery and implantation of the keratin sponge are represented in Figure 13d (left). The footprint changes in two groups of control and keratin, where their damaged nerve was distorted by keratin sponge, were evaluated after 3, 7, 10, 13, 17, and 21 days from surgery (Figure 13d(right)). Keratin has also been used in combination with other proteins to enhance the quality of the scaffolds produced. For instance, biocomposite scaffolds based on jellyfish-derived collagen, human hair-derived keratin, and eggshell-derived nano-hydroxyapatite (nHA) were fabricated by the freeze-drying method for bone tissue engineering (Arslan et al. 2017). When comparing the collagen-keratin-nHA scaffolds to the keratin-free scaffolds, Alizarin red histochemical staining revealed calcified matrix formation by the cells on the collagen-keratin-nHA scaffolds.(Arslan et al. 2017). In another study, Naderi et al. evaluated the effect of chicken feather-derived keratin on the physical, mechanical, and biological properties of poly (3-hydroxybutyrate) electrospun scaffolds, particularly for bone tissue regeneration (Naderi et al. 2020). These examples collectively reveal the potential capabilities of keratin in fabricating scaffolds for tissue engineering, either alone or in combination with other biopolymers. In another study, human hair keratin NPs were used to control doxorubicin release. Keratin NP size showed a narrow size distribution with PDI and an average diameter of 0.108 and 214.8 nm, respectively. Guidotti et al. prepared wool keratin-polybutylene succinate nanofibrous mats to study the drug release behavior of such carriers for diclofenac (Figure 13e (left and middle)) (Guidotti et al. 2020). Pure polybutylene succinate mats and blended keratin mats released 15.3 and 165.2 $\mu g.cm^{-2}$ of the drug after 6 h, respectively. The release after 8 h was ~10 times higher in the case of blended mats (Figure 13e (right)), showing that keratin incorporation increased the drug release rate of the nanofibrous due to the repulsive phenomena between negatively charged keratin and negatively charged diclofenac, as well as the narrower diameter distribution of keratin-based mats, compared to that of pure polybutylene succinate mats which facilitates drug diffusion.

The keratin extracted by denaturation method has a higher molecular weight, mechanical properties, lower polarity, and lower solubility than keratin extracted via degradation methods. Therefore, for biomedical applications that require higher mechanical properties and lower degradation rates, such as bone, nerve, and cardiovascular tissues, keratin extracted by denaturation methods can be used. In contrast, keratin extracted by degradation methods has good potential for wound dressings, cartilage, and drug delivery. Nevertheless, the keratins extracted from both methods have been used in various biomedical applications (Tables 4 and 9). In addition to the extraction method, keratin source influences ultimate properties; rheological properties of feather keratin are more than wool and hair. The properties of scaffolds based on keratin can be tunable by molecular alteration weight, extraction method, modification with functional groups, adding nanoparticles, and other polymers. Although various forms of keratin scaffold showed cell viability and proliferation, further investigation is needed to better understand how they interact. Clinical studies of the effectiveness of keratin in biomedical applications as well as development of developing a new green method for keratine extraction with a high recovery percentage while preserving its structure could be the next step.

Silk fibroin

Some outstanding features that highlight the potential applications of silk fibroin for tissue engineering are high mechanical strength, biocompatibility, stability to heat and humidity, high oxygen permeability, and tunability (Costa, Silva, and Boccaccini 2018a). In 2019, for the first time, a scaffold made up of solubilized or reconstituted silk protein, known as Silk Voice, was approved by the food and drug administration (FDA) (Chouhan and Mandal 2020). A novel bioactive film was produced based on silk fibroin and paramylon to mimic the properties of the ECM. The effect evaluation of pure and blended films on HEK 293 T cells' viability revealed that the samples did not show any noticeable toxicity with at least 90% viability compared to the respective controls (Arthe, Arivuoli, and Ravi 2020). The raw tussah silk film was investigated for its potential tissue engineering applications in another study; MTT results affirmed that water-rinsed silk film has higher cell survival than the control sample at at 2 and 66 days after cell seeding (Zhang et al. 2019). The effect of elastomeric polyurethane

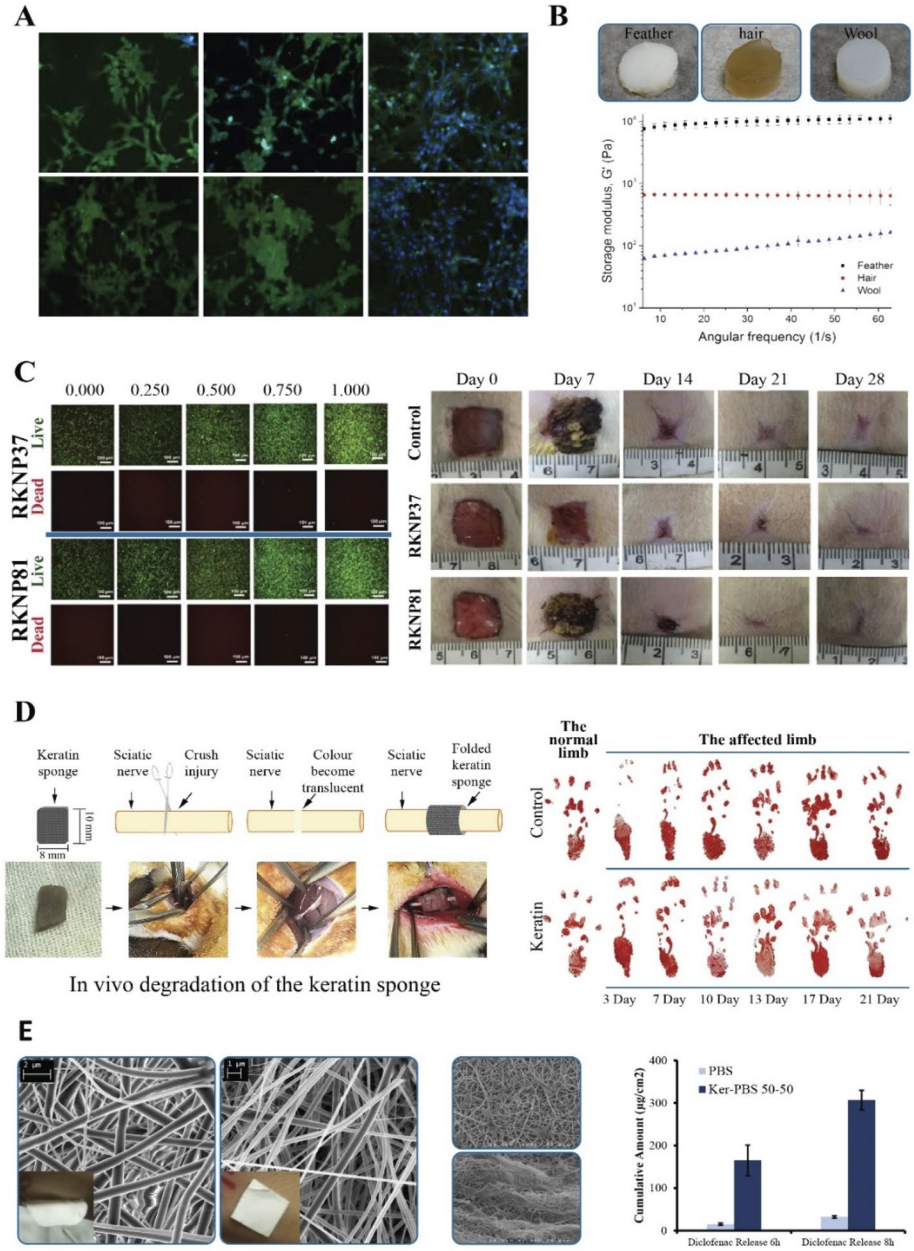

Figure 13. A) Fluorescence microscopic images of Calcein AM and DAPI staining of NIH3T3 cells at 3, 5, and 7 days after cells seeding on collagen and keratin (Reprinted from (Ramya, Thangam, and Madhan 2020) with permission from Elsevier), B) Color photograph and storage modulus-frequency sweeps of keratin extracted from feather, wool, and hair (Reprinted from (Esparza et al. 2018) with permission from Elsevier), C) Fluorescent images of live and dead HaCaT cells treated with various human type I hair keratin 37 and human type II hair keratin 81 nanoparticles (NPs) concentration after 24 h of incubation(left), healing progression and rate of wound closure wound treated with human type I hair keratin 37, human type II hair keratin 81, and keratin nanoparticles (NPs) on days 0, 7, 14, and 28 (right) (Reprinted from (F. Gao, Li, et al. 2019) with permission from ACS Publications), D) a schematic diagram of surgery and the corresponding surgical photographs of repair of sciatic nerve injury by human hair keratin sponge (left) and the footprint changes images after 3, 7, 10, 13, 17, and 21 of surgery in the control group and keratin group that their damaged nerve was warped by human hair keratin sponge (right) (Reprinted from (J. Gao, Zhang, et al. 2019), Springer nature, open access), E) Visual images and scanning electron micrographs of poly(butylene succinate) and keratin- poly(butylene succinate) 50-50 (left), SEM micrograph of NIH-3T3 on poly(butylene succinate) and keratin- poly(butylene succinate) 50-50 (middle), cumulative amount (µg/cm2) of diclofenac sodium released from poly(butylene succinate) patch and keratin- poly(butylene succinate) 50-50 patches after 6 and 8 hours. Error bars represent mean ± SD. (right) (Reprinted from (Guidotti et al. 2020) with permission from Elsevier).

type and ratio on the physicochemical properties of electrospun polyurethane/silk fibroin extracted from natural silkworm hybrid nanofibers has been studied as potential scaffolds for tissue engineering. With an increasing concentration of silk from 0 to 100%, the tensile strength increased from 1.3 to 3 MPa while the Young's modulus increased from 1 to 40 MPa. The proliferation of fibroblast cells from human neonatal foreskin increased along with the culture time, as revealed by MTT assay, and hematoxylin-eosin (H&E) staining images (Figure 14a). The cells proliferation was also increased by increasing silk content in the nanofibrous scaffolds (Dehghan-Manshadi et al. 2019).

In bone tissue engineering, biodegradable scaffolds ought to possess high mechanical and osteogenic properties,

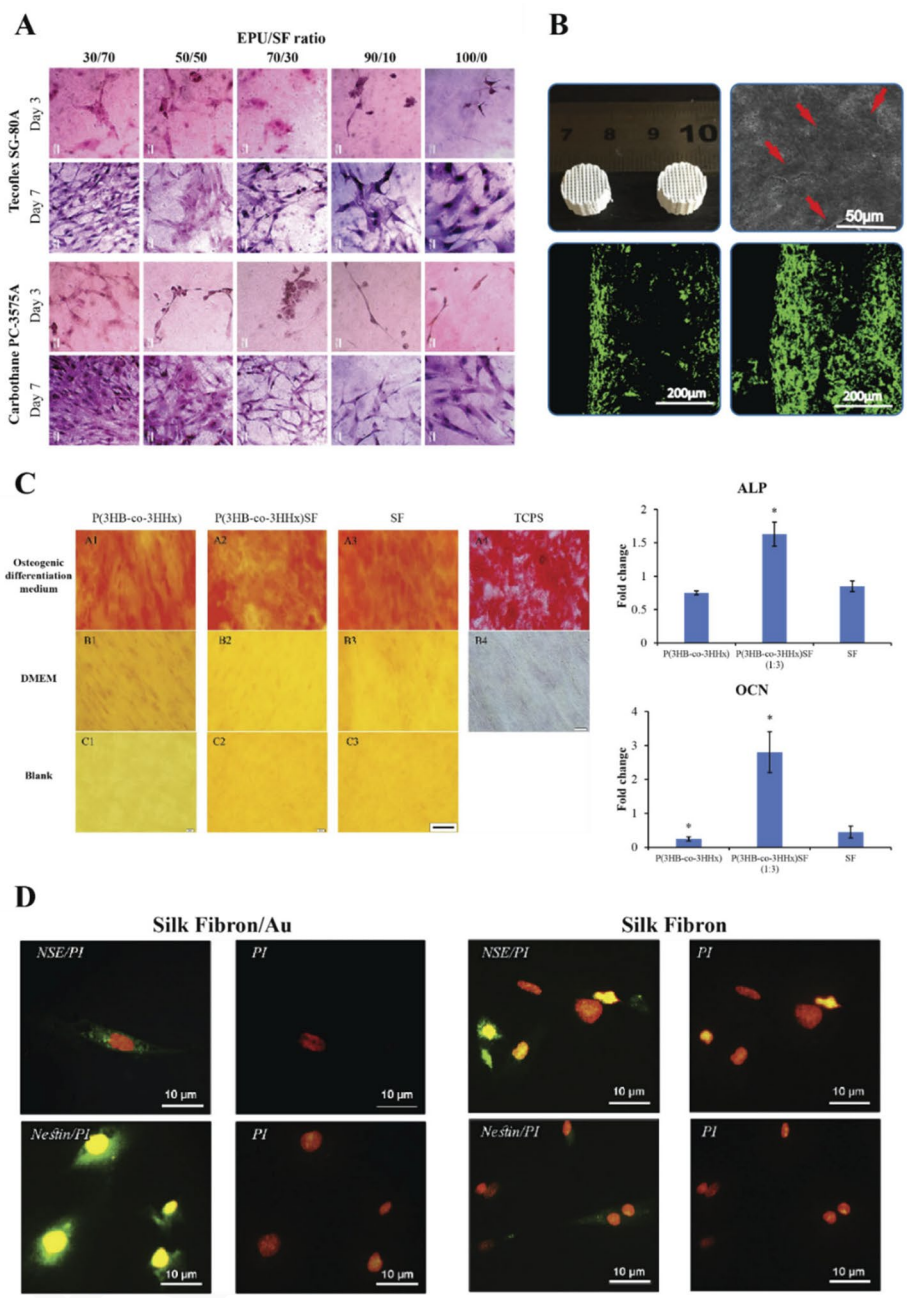

Figure 14. A) Hematoxylin-eosin (H&E) staining micrographs of fibroblast cells from human neonatal foreskin (YhFF#8) cells cultured on polyurethane/silk fibroin extracted from natural silkworm hybrid nanofibers scaffolds with various ratios for 3 and 7 days (Reprinted from (Dehghan-Manshadi et al. 2019) with permission from Elsevier), B) optical image of cocoon-derived silk fibroin scaffolds combined with mesoporous bioactive glass by using 3 D bioprinting (top, left), SEM image of hBMSCs attached on bioactive glass/silk fibroin composite scaffold after 7 days (top, right), confocal laser scanning microscopy images of cells seeded on mesoporous bioactive glass/silk fibroin composite scaffolds for 1, and 7 days. (bottom) (Reprinted from (Du et al. 2019), Elsevier open access), C) Histological analysis of osteogenic differentiation of the human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) with Alizarin Red staining at day 21 on poly(3-hydroxybutyrate-co-3-hydroxyhexanoate), poly(3-hydroxybutyrate-co-3-hydroxyhexanoate)/silk fibroin, and silk fibroin cultured in osteogenic differentiation media, DMEM, and blank media (left), qPCR analysis of gene expression level of alkaline phosphatase (ALP) and osteocalcin (OCN) during osteogenesis on poly(3-hydroxybutyrate-co-3-hydroxyhexanoate), poly(3-hydroxybutyrate-co-3-hydroxyhexanoate)/silk fibroin, and silk fibroin at day 21 after the human umbilical cord-derived mesenchymal stem cells seeding (right) (Reprinted from (Ang et al. 2020) with permission from Elsevier), D) Immunocytochemistry staining (primary antibody to nestin and NSE (green), nuclei stained by PI (red)) of PC12 cells on gold nanorods reinforced silk fibroin nanocomposite and silk fibroin scaffolds (Reprinted from (Afjeh-Dana et al. 2019) with permission from Elsevier).

whereas silk fibroin has been suggested as an ideal material for bone scaffolds (Zhang et al. 2014; Du et al. 2019; Ang et al. 2020; Cao, Wang, et al. 2020). Du et al. fabricated various cocoon-derived silk fibroin scaffolds combined with mesoporous bioactive glass (Du et al. 2019) using 3 D bioprinting for bone tissue engineering (Figure 14b). The expression of bone morphogenetic protein-2 (BMP-2) on composite scaffolds was ~ 22 folds higher compared to the control scaffolds indicating that the composite could enhance osteogenic differentiation. Similarly, osteocalcin (OCN) expression showed much higher expression on the composite scaffolds. In another work, osteogenic differentiation of

Table 10. The underlying mechanism, advantage, and disadvantage of common extraction methods for collagen. Q12

Methods	Mechanism	Chemicals	Advantages	Disadvantages	Ref
Salting out method	Collagen proteins have the properties of salt soluble and salting out.	NaCl, citrate, phosphate, and Tris-HCl solution	It is suitable for type I collagen precipitation	Unstable Limitation in utilization	(Gendaszewska et al. 2016)
Alkali method	Hydrolysis (large amounts of hydrolyzed collagen proteins are produced).	NaOH, Na_2CO_3, and MnO_2.	Simple techniques Easy to handle Mild reaction Fast hydrolyzation	Water, air, and soil pollution Long cycle extraction process. Corrosion of equipment	(Jafari et al. 2020; Gendaszewska et al. 2016)
Acid method	Destroy the salt bonds between molecules and Schiff bases	AcOH, citric acid, or hydrochloric acid.	High yield Fast hydrolyzation	Corrosion of equipment High pollution Damage to the collagen structure	(Devita et al. 2021; Abasi, Naghdi, and Mousavi Nadushan 2021; Jafari et al. 2020; Gendaszewska et al. 2016)
Enzymatic method	Enzymes act on non-helix peptide chains of collagen protein	Pepsin, papain, trypsase.	Selectivity at reaction Less damage to collagen structure High purity Stable physical and chemical properties Mild condition	Hydrolysis is not complete. Reaction time is extended. De-chroming is required. High cost	(Devita et al. 2021; Abasi, Naghdi, and Mousavi Nadushan 2021; Pap et al. 2022; Gendaszewska et al. 2016)
Microbial method	Fermentation by reproduced microbial	Microbe	Cheaper than the enzymatic method,	Low yield	(Zinina, Merenkova, and Galimov 2021; Zhang et al. 2022)
Ultrasound	Shear and cultivation	Ultrasound wave, ultrasonic	Low cost, high yield, simple operation, and time-saving	–	(Shaik, Chong, and Sarbon 2021; Petcharat et al. 2021)
Microwave	Converting microwave energy to heat energy	Microwave	Low cost and simple treatment process improve the extraction yield	–	(Feng et al. 2022;Viji et al. 2022; Feng et al. 2021)
High hydrostatic pressure	Cleavage of the intra bonds between the collagen structure		Green method, short time,	High cost, damage to the protein structure	(Bolat et al. 2021; Rýglová et al. 2021)
SFE	High-pressure cleavage, the protein covalent bonds	CO_2, high pressure	Environmentally friendly, high yield,	High cost, and lack of products safety	(Liu, Tao, et al. 2021; Thirukumaran et al. 2022)

human umbilical cord-derived mesenchymal stem cells on electrospun poly(3-hydroxybutyrate-co-3-hydroxyhexanoate)/silk fibroin derived from *B. mori* cocoons was investigated (Figure 14c). Mesenchymal stem cells (MSCs) gene expression analysis revealed the up-regulation of ALP (1.6-fold) and OCN (2.8-fold) on the electrospun scaffold when compared to the control sample (Figure 14c) (Ang et al. 2020). In addition to bone tissue engineering, silk fibroin has also been used in other musculoskeletal tissues such as cartilage and muscle (Hong et al. 2020; Singh, Bandyopadhyay, and Mandal 2019; Zhang, Qu, et al. 2021). For instance, wang et al. (Wang, Sun, et al. 2019) prepared a *B. mori*-derived silk fibroin/collagen/hyaluronic acid scaffold incorporating pilose antler polypeptides microspheres via admixing, cross-linking, and lyophilizing processes. Pilose antler polypeptides microspheres significantly improved bone marrow stromal cell proliferation and cartilage tissue regeneration. To investigate the potential application of silk fibroin for nerve tissue engineering, Afjeh-Dana et al.(Afjeh-Dana et al. 2019) evaluated the proliferation and attachment of PC12 cells on *B. mori* extracted silk fibroin reinforced gold nanorods scaffolds; incorporating gold nanorods into silk fibroin scaffolds significantly increased the electrical conductivity of the bulk scaffold from $12.5\,\beta\,10^9$ to $1.0\,\beta\,10^8$ ohm. A higher expression level of neuron-specific enolase and neural-specific proteins like nestin was observed in the immunocytochemistry staining on the silk fibroin/gold nanorods nanocomposites than neat silk fibroin scaffolds (Figure 14d). Kim et al.(Kim, Yeon, et al. 2018) created a bioink for digital light processing 3 D bioprinting based on silk fibroin methacrylation, which was produced by using glycidyl methacrylate during the silk fibroin solution preparation, for tissue engineering applications.

Hydrophilic and hydrophobic amino acids of silk fibroin empower this amazing material for NPs preparation using a self-assembling process (Ghalei et al. 2020). Moreover, because of its tunable β-sheet crystalline formation, drug encapsulation and release properties could be controlled (Wu et al. 2020). Therefore, silk fibroin has been widely investigated for NPs fabrication and drug delivery (Kucharczyk et al. 2021; Pandey et al. 2020). Solomun et al. examined the effect of silk processing conditions and two fabrication methods on the physicochemical properties of the ensued NPs (Solomun et al. 2020). They used sodium carbonate for silk degumming and evaluated the effect of degumming time on the NPs size and polydispersity index (PDI). The result showed that longer degumming (60-90-minute) results in 100-114 nm particle size and narrow particle

size distribution. In contrast, shorter degumming time (10 minutes) leads to larger particles (~168 nm) and broader particle size distribution. They did not observe any significant differences between particle size and PDI of silk NPs produced by microfluidic and manual dropping methods. However, the NPs generated via the microfluidic system had significantly lower zeta potential (−28 to −29 mV) compared to those prepared by manual dropping protocol (−39 to −43 mV) (Solomun et al. 2020). Zhuang et al. investigated the influence of silk fibroin microparticles on biomedical grade polyurethane filament's physical properties and drug release behavior (Zhuang et al. 2019); hybrid filament with 5 wt% silk fibroin microparticles showed the highest drug loading, ~ 3.5% after 48 h from loading time. All samples with different concentrations of silk fibroin microparticles showed a burst release of drug in initial releasing time followed by a continuous release from 10 to 72 h. Due to their high aspect ratio, micro/nanofibers have exhibited great potential in drug delivery applications (Ghaffari-Bohlouli et al. 2020; Dadras Chomachayi et al. 2018; Zhang et al. 2016) as thin (nanoscale), smooth, and bead-free fibers are more suitable (Ghaffari-Bohlouli et al. 2020); electrospinning, self-assembly, and phase separation being the primary protein-based micro/nanofibers production methods (DeFrates et al. 2018; Yıldız, Kara, and Acartürk 2020). Electrospun nanofibers of silk fibroin (from *B. mori*) and gelatin were fabricated with different concentrations of gelatin for controlled release of thyme essential oil and doxycycline monohydrate. Using a concentration-dilution method, silk fibrin has been demonstrated to be assembled into nanofibers (Figure 15a (left))(Lu et al. 2012). This method includes a concentration and dilution process followed by incubation at 60 °C for 24 h to obtain silk fibroin nanofibers. By implementing this method, Ding et al. fabricated silk fibroin nanofibers for sustained delivery of a pro-angiogenesis drug, desferrioxamine (DFO) (Figure 15a (right)) (Ding et al. 2019). Their results showed that this nanofibrous system could provide a sustained release of DFO over 40 days; this extended and sustained release prevents DFO burst release toxicity. In another interesting methodology, core-shell nano/micro-fibers have been produced to preserve sensitive drugs and bioactive molecules in their structure and control

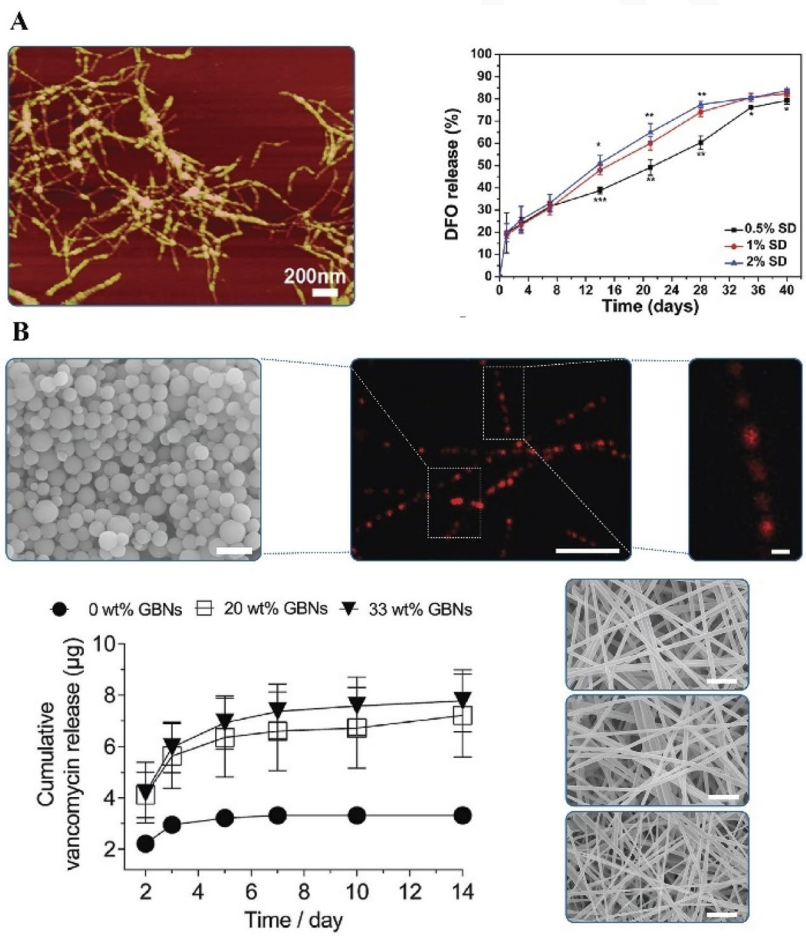

Figure 15. A) Silk fibroin nanofiber loaded by pro-angiogenesis drug desferrioxamine (DFO) fabricated by concentration-dilution process (left) and DFO release profile for nanofibers loaded with different amounts of the drug (SD) represents silk fibroin nanofibers loaded with DFO) (right) (Reprinted from (Z. Ding et al. 2019) with permission from ACS Publications). B) SEM photograph of gelatin type B nanoparticles (GB-NPs) with (scale bar is equal to 500 nm) (top, left) and confocal microscope images of fluorescent died GB-NPs embedded silk nanofibers (scale bar is equal to 10 μm in f and 1 μm) (top, right) (Song et al. 2017), B) Vancomycin release profile from composite nanofibers with different concentrations (0, 20, 33 wt%) of GB-NPs during 14 days (left), and SEM photographs of electrospun silk nanofibers loaded with 0, 20, and 33 wt% GB-NPs, respectively (scale bar is equal to 4 μm) (right) (Reprinted from (Song et al. 2017) with permission from Wiley).

their release rate (Babitha et al. 2017; Ojah et al. 2019; Pant, Park, and Park 2019). Song et al. produced silk-based nanofibers embedded with vancomycin-loaded gelatin type B NPs (VG-NPs) by electrospinning technique (Song et al. 2017). It has been postulated that negatively charged nanomaterials could sustainably release positively charged drugs like vancomycin. The confocal microscopy images revealed that the VG-NPs were successfully embedded within the silk fibroin-based fibers (Figure 15b (top, left, and top, right)); changing silk per NPs ratios, resulted in the formation of fine and bead-less fibers. Their results showed that incorporating negatively charged VG-NPs into silk-based nanofibrous scaffolds provides more sustain release than direct use of vancomycin into nanofibers (Figure 15b (bottom)). Yavuz et al.(Yavuz et al. 2020) fabricated MN patch for delivery of levonorgestrel (LVN) using bombyx mori derived silk fibroin and simply by varying the sodium carbonate treatment time, obtained low, medium, and high molecular weight silk fibroins. They found that while the molecular weight of extracted silks does not significantly affect the MNs release profile, increasing the silk concentration slowed the MNs release rate. Zhu et al. investigated a composite MN patch with silk fibroin/insulin needles and proline/silk fibroin/insulin as their pedestal for insulin delivery using the micro-moulding method (Mingmei Zhu, Liu, et al. 2020). The Bombyx mori-derived silk fibroin MNs possess adequate mechanical properties to penetrate the skin. The dissolvability of silk fibroin provides a rapid insulin release, while the support could provide a sustained release via the cavities created by MNs insertion. The silk fibroin MNs showed good storage stability for insulin, preserving more than 90% of its biological activity after 30 days.

Due to its unique hierarchical structure, Silk fibroin has an excellent mechanical strength that can be used in all biomedical applications, especially bone tissue engineering. Other properties of silk fibroin such as biodegradability, hydrophilicity, B-sheet content, materials morphology, solution behavior, and cell interactions can be tuned by its modification chemistries, which expand its utility in a wide variety of biomaterials applications. Moreover, silk sericin is a natural polar polymer that can be readily crosslinked and conjugated with other polymers, can act as a moisturizing agent, increase cell interactions, can facilitate the migration and proliferation of collagen type I in the skin is used in wound healing and epithelial repair. Easy, effective, and low-cost extraction of silk fibroin and silk sericin and their potential in biomedical application increase researcher attention to employing them in nanofabrication, 3 D printing, smart drug delivery, and multilevel modification technologies. However, many attempts to find sustainable, eco-friendly, economical technologies and devices and clinical investigations are needed for large-scale and industry applications.

Biomedical application

Although animal by products can be used in a variety of biomedical applications, due to their biocompatibility and biodegradability, they are almost exclusively used for specific tissue and targets due to their intrinsic and natural nature feathers such as hydrophilicity, mechanical and thermal properties, solubility, molecular weight, amino acid composition and content, the interactions with host tissue. Due to their hydrophilicity, weak mechanical properties, and high capacity for water absorption, collagen, gelatin, and silk sericin have been demonstrated to be useful in wound dressing, skin regeneration, and tissue repair. Not only they are nontoxic and have desired cell viability, but they can also improve re-epithelization in skin regeneration and wound healing applications by enhancing collagen production via keratinocytes via the proteins like silk fibroin and keratin, on the other hand, are more stable against the thermal and harsh conditions and have good mechanical strength, making them a good candidate for bone tissue, nerve tissue, and drug delivery applications due to their high molecular weight and hydrogen and disulfide bonds intertwined in inter their structure. Sources and extraction methods, on the other hand, have a remarkable effect on the final properties of protein. For example, marine collagen has a lower immunological immunology response than mammalian collagen, while feathers keratin has better mechanical qualities than wool and hair keratin.

Furthermore, some extraction methods can damage the protein's structure and cause it to degrade into lower molecular weight protein, lowering the mechanical properties. Acetic, basic, and even enzymatic protein extraction methods are in this category. Therefore, regardless of the source, extraction, or recovery method, each protein can have a wide range of properties and be used in a variety of biomedical applications. Moreover, proteins have different amino acids in their structure, which allows them to be modified modify with functional groups, other polymers, and additives to tune and change their properties and expand their application. Further investigations are missing here to find how cells interact with protein-based scaffolds and how to improve their properties. Also, their efficacy in clinical tests must be demonstrated before they may be also used on a large basis.

Conclusions and future prospective

As the human population grows, the demand for foods; especially proteins, which are a vital ingredient of body energy, increases. As a result, a tremendous amount of food wastes is produced which with current approaches, not only requires a large area to landfill, but also generate green gases, pollute the earth, and underground waters, spreads a spread variety of disease. Therefore, it is critical to make effort to reduce food waste and develop methods and approaches for recycling and reusing it. Although waste can be converted to heat and valuable gases through recycling process such as burning and anaerobic digestion. Animal waste possess high-value components, including polysaccharides, proteins, and unsaturated fats that can be extracted and reused as human and animal feed, pharmaceutical, and biomaterials in biomedical applications. Collagen, gelatin, elastin, keratin, silk fibroin, and sericin are some of the most common proteins that can be extracted extractable from animal by-products.

Removing the undesired materials and preparing the animal by-products for extraction is the first step. Then, one extraction method is employed regarding the target protein, desired properties, and available chemicals and equipment. For each protein, many extraction methods have been reported that generally, traditional methods have a low yield, low cost, severe conditions (using toxic chemicals or high temperature), long processing time, harmful downstream waste that damage protein structure. Hence, some new, eco-friendly, economic technologies and methods with high extraction rates, more minor side effects on protein structure, and recyclable and reusable wastes have been introduced, such as supercritical fluid extraction, deep eutectic solvent, and ionic liquids. In addition, to improve protein yield from animal by-products, combining traditional methods with new technologies or using pretreatment methods following extraction methods has been suggested. Acidic, alkalic, enzymatic, ultrasonic, and microwave irradiation are some pretreatment methods used for protein extraction and sometimes can be used together. To recover extracted and isolated proteins, methods like spray and freeze drying, salting in and out, gradient pH, and filtering can be employed to separate them from solvents, chemicals, and impurities. Although the efforts to develop green and highly efficient protein extraction methods have yielded promising results, further research and study is needed to achieve sustainable, ecofriendly, and cost-effective approaches that can be scaled up.

Biocompatibility, biodegradability, and the ability to design in different forms are common feathers of extracted proteins from animal by-products, making them good candidates for biomedical appliances. Their intrinsic properties have been used in divorce tissue engineering and drug delivery applications, with promising results. Moreover, a variety of protein modification have been reported to tune and change their properties to access scaffolds with a similar feather as target tissue. Due to the ability to extract protein from animals by products to manufacturing, they are used in many forms such as films, nanofibers, 3 D printed scaffolds, nano, microparticles, etc. Their applications can be expanded by using them as a carrier of cells and growth factors. Although all proteins extracted, have been illustrated good cell attachment, viability, and proliferation, their interaction with different cells is missing. Also, it is necessary to investigate their clinical potential before applying them on a large scale and in the industry.

List of abbreviation

FAO	Food and Agriculture Organization
IFCO	International Food Container Organization
ECM	Extracellular matrix
Bombyx mori	B. mori
ASC	Acid-soluble collagen
PSC	Pepsin-aided acid soluble collagen
DES	Deep eutectic solvent
COD	Chemical oxygen demand
BOD	Biological oxygen demand
HBA	Hydrogen bond acceptor
HBD	Hydrogen bond donor
SFE	Supercritical fluid extraction
DSC	Differential scanning calorimetry
AcOH	Acetic acid
NaOH	Sodium hydroxide
FDA	Food and drug administration
BMP-2	Bone morphogenic protein 2
EDC/NHS	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide in the presence of *N*-hydroxysuccinimide
OCN	Expression of osteocalcin
ALP	Alkaline phosphatase
MSCs	Mesenchymal stem cells
HA	Hydroxyapatite
SEM	Scanning electron microscopy
BMSCs	Bone mesenchymal stem cells
hUC-MSCs	Umbilical cord mesenchymal stem cells
CCK-8	Cell counting kit 8
G′	Storage modulus
G"	Viscous modulus
PBS	Phosphate-buffered saline
MW	Microwave
ILs	Ionic liquids
MN	microneedle

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