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Protein Hydrogels: A Concise Review of Properties and Applications

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Abstract
Proteins are renewable resources generated from residues and byproducts of the agriculture and livestock industries. Numerous in-depth studies have been conducted on proteins for their utilisation as protein-based hydrogels. Henceforth, for maximum enrichment of these dietary proteins in the diet, available proteins are transformed into hydrogels using enzymes, chemicals, or physical means. In addition to being nontoxic, biocompatible, biodegradable, accessible, and renewable, protein hydrogels are also affordable. They come in a wide range of physicochemical states dissolved in emulsions or liquids, like particle hydrogels, macro hydrogels, a form of gel colloid, and suspensions. However, composite or hybrid hydrogels are developed by mixing proteins with polysaccharides and other biomolecules to enhance mechanical and functional properties for specific applications. Additionally, these biomaterials have attracted increasing interest in the past few years owing to their improved tensile strengths and can enclose preserved and released biomolecules. Thus, hydrogels can manage the release of bioactive substances and boost the bioavailability of such ingredients, in addition to their capacity to heal wounds and their use in the food and agriculture industries. This article thoroughly analyses basic polymer hydrogel categorization, diverse protein hydrogel forms, production techniques, physicochemical and functional properties, and applications in various fields. This review also sheds light on methods for determining the shape, thermal stability, and rheological characteristics of protein-based hydrogels. Therefore, will provide a comprehensive reference for the numerous aspects of protein hydrogels that are important to multiple academic and industrial disciplines.

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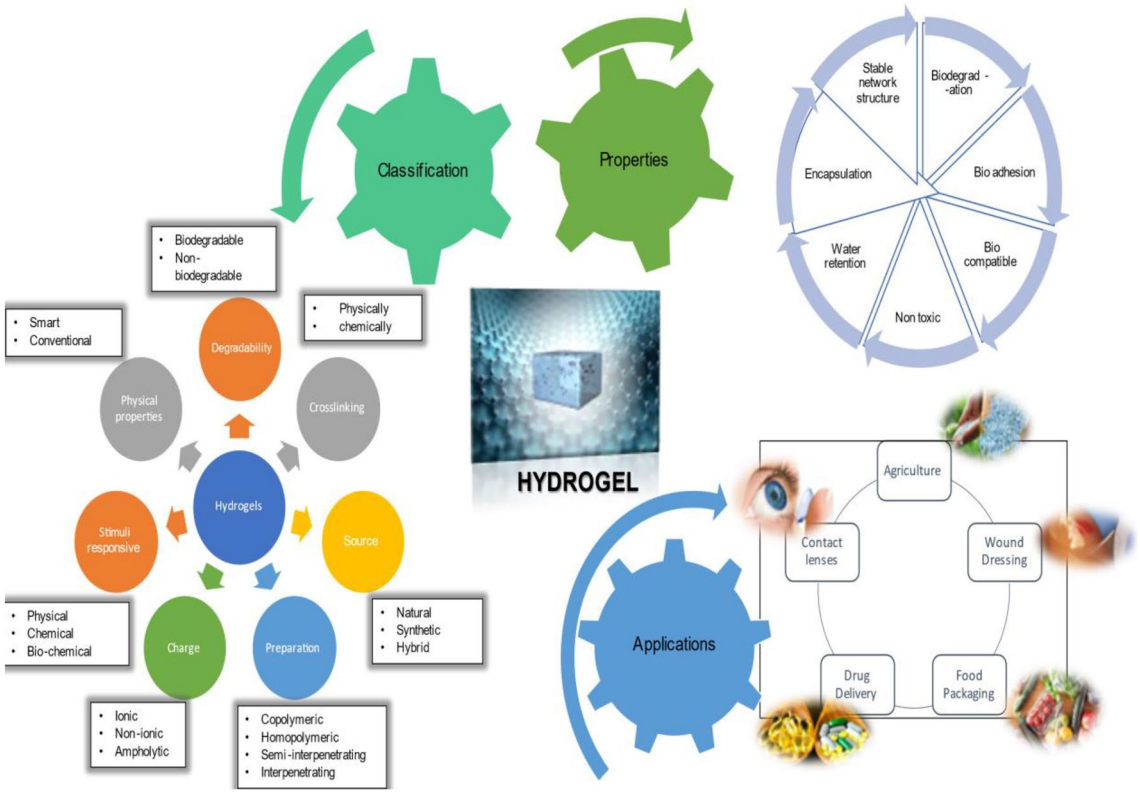
Graphical Abstract



Keywords Hydrogel · Protein · Polysaccharide · Biomaterials · Material science

Introduction

The term "hydrogel" was first applied in 1894 in a publication citing its usage as a protein-rich source. Also, the article referred it to be a colloidal gel consisting of inorganic salts rather than a hydrogel as we understand it today. Furthermore, a polyhydroxy ethyl methacrylate (pHEMA) hydrogel was invented a long time afterwards, in 1960, intending to employ them in long-term applications involving human tissues, and was the first cross-linked network material that was reflected in the scientific literature. It was characterized by its standard hydrogel properties, one of which is high water affinity (Chirani et al. 2015). Since then, numerous studies have been conducted on hydrogels and presented their vast applications. The term hydrogel is composed of two words, i.e., hydro (water) and gels (thick, soft-cum-semirigid, and transparent colloidal dispersion) and has been well-defined in various manners by scientists over the years. The most prevalent is "hydrogels or hydrophilic gels," having a three-dimensional structure composed of a single monomer or polymer chain of networks. The hydrogel is flexible and can be made into a variety of forms and sizes. It can also absorb up to a thousand of its dry weight in water (Seliktar 2012). Another description is that it is a polymeric substance that can absorb a lot of water inside its network but won't dissolve (Ahmed 2015). A hydrogel can be produced using any method that produces a cross-linked polymer. When hydrophilic monomers and a multipurpose cross-linker are combined, copolymerization/cross-linking free-radical polymerizations are frequently utilised to create hydrogels (Ullah et al. 2015). Due to counter-balanced capillary, osmotic, and hydration forces, polymeric chain networks interact with water or biological fluids, causing the chain network to expand. This equilibrium state in the hydrogel is determined by the degree of these opposing effects, which dictates some of the hydrogel's inherent qualities, such as internal transport, diffusion properties, and mechanical strength (Varaprasad et al. 2017). Based on certain characteristics such as swelling rate, mechanical capabilities (for food packaging and pharmaceutical applications), and biocompatibility (essential for edible hydrogels), hydrogels can also be employed in a variety of industries (Ali and Ahmed 2018). Hydrogels impart a wide range of food and non-food applications such as carriers for flavour, bioactive & nutritional

compounds; enhance bioavailability; provide stable network structures; improve stability; calorie reduction; trans & saturated fat replacements in dessert; oral delivery of lipophilic active ingredients; tissue engineering; wound dressing; contact lens; disposable diapers; pharmaceutical industry; agriculture; etc. (Caló and Khutoryanskiy 2015; Li et al. 2016; Pyarasani et al. 2019; Sabbagh et al. 2019). Moreover, the characteristics of hydrogels depend upon several factors like polymer concentration, the degree of crosslinking, temperature, pH, age, salt concentrations, etc. (Bae and Kurisawa 2016; Saini 2017; Gun'ko et al. 2017). Synthetic polymers including poly acrylamide, poly hydroxyalkyl methacrylates, poly acrylamide, and polymethacrylamide, as well as its derivates poly N-vinyl-2-pyrolidone and polyvinyl alcohol (PVA), are used to make hydrogels. Despite having good mechanical strength and great water absorption capabilities, synthetic hydrogels have certain unpredictability of their toxicity references caused by the unresponsive monomers in the gel's structure, which refrains their usage.

In addition, the shortcomings offered by synthetic hydrogels in terms of their poor biodegradability and biocompatibility could also pose environmental issues (Ni and Dumont 2017). Henceforth, it is preferable to utilize natural biopolymers like protein, which can quickly produce functional colloids since they are safe for humans and environment-friendly. Polysaccharides and proteins are the constituents of the majority of natural hydrogels. When creating hydrogels, proteins have an advantage over polysaccharides because they have more functional groups available for modification (amino, thiol, hydroxyl, and carboxyl), are delivered more sensitively to external stimuli, have a unique ability to recognise some peptides and can self-assemble (Ren et al. 2017; Cai et al. 2017; Zhang et al. 2013). Edible proteins have been considered prominent in the emergence of functional colloidal gels, including targeted specific delivery of bioactive substances and modification of food-body interactions to strengthen nutritional absorption rate, digestion, and oral perspective (McClements 2017). The functional groups inside proteins include carboxyl, amino, hydroxyl, phenolic, and sulfhydryl, which offer many potential applications in the food and drug industries. These may serve as reactive sites for chemical reactions and widen the food, non-food and other biomedical applications. The cross-proteins are safe to eat, compatible with other organisms, and break down naturally. Peptides and proteins are consistently included in hydrogels for creating imitation substances for tissue engineering and medication delivery since the polypeptides are an integral component of the extracellular matrix (Singhal and Gupta 2016). Also, bestowing unique properties, such as foaming, water binding, and thickening, protein-based hydrogels are extensively utilized in various food applications (Gorji et al. 2014; Zhang et al. 2020; Abaee et al. 2017). Food protein-based hydrogels from casein, whey protein, keratin, gelatin, collagen, plant protein, etc., can be made unaided or combined with other food-grade polymers. However, protein also imparts biocompatibility, non-toxicity, and availability of reactive sites for alteration, as they contain most hydrophilic functional groups. This review aims to determine protein-based hydrogels, initiated with a brief description of native hydrogels and their classification based on different characteristics followed by different types of proteins utilised for hydrogel preparation and their properties are discussed at length. As hydrogels have tunable viscoelasticity and are biocompatible and injectable, based on these features, their applications in biomedical, food and agricultural fields are discussed.

Classification of Hydrogels Based on Different Parameters

Different categories of hydrogels exist (Fig. 1) based on their physical qualities, manufacturing process, swelling characteristics, ionic charges, origin and sources, cross-linking nature, rate of biodegradation, etc. (Ullah et al. 2015).

Based on the Source

There are three broad groups of hydrogels based on the source, i.e., natural, synthetic and hybrid. Protein-based materials, polysaccharide-based materials, and those formed from de-cellularized tissue are examples of naturally derived hydrogels wherein natural gels are primarily composed of proteins. The extracellular matrix components like chitin make them naturally biocompatible, bioactive, and potentially suitable for various biomedical applications (Catoira et al. 2019), Whereas synthetic polymers like polyamide (PA) and polyethylene glycol, also known as PEG, are the source of synthetic hydrogels. These are the further different kinds of synthetic monomers: anionic, like those made from acrylic acid or crotonic acid; and cationic, like vinyl pyridine, which comes from aminoethyl methacrylate; and neutral, like hydroxyl alkyl methacrylates made from acrylamide, N-vinyl pyrrolidone, and hydrophobic acrylic (Li et al. 2007). These biocompatible polymers are hydrolysed either enzymatically or non-enzymatically, or both, in vivo to disintegrate them. The biocompatibility and biodegradability of such polymers also often depend on altering their surface hydrophilicity (Gyles et al. 2017). Hybrid/composite hydrogels are produced by combining synthetic polymers with natural ones to overcome the aforementioned problems, enhance current formulations, and broaden the scope of potential uses (Zhu et al. 2018). Generally speaking, proteins and peptides incorporated into networks react with synthetic polymers through polymerization or conjugation to create hybrid hydrogels for a variety of experimental applications

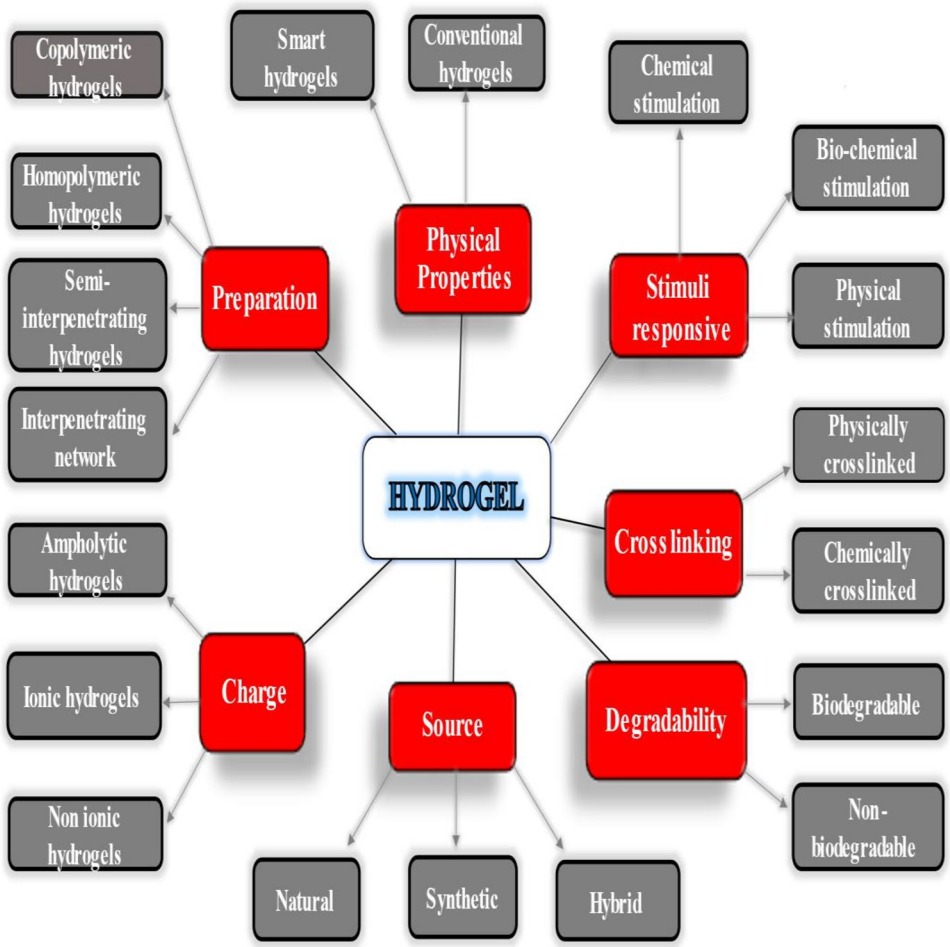


Fig. 1 Classification of hydrogels based on various attributes

(cell proliferation, differentiation, and migration investigations) and in-vivo (wound healing, tissue restoration, and drug delivery) (Palmese et al. 2019).

Based on the Charge

Hydrogels are also available based on their non-ionic, ionic and ampholytic nature wherein the backbone and side groups of the non-ionic hydrogels are chargeless (Fig. 1). Water-polymer interactions cause these non-ionic hydrogels to swell in aqueous medium wherein Poly acrylamide, polyhydroxy ethyl methacrylate, PVA, and PEG are examples of non-ionic hydrogels (Singhal and Gupta 2016). Cationic (positive charge carrying) and anionic (negative charge carrying) hydrogels are examples of ionic hydrogels. The pH of the aqueous medium, which controls the level of ionic chain dissociation, controls swelling in the first scenario. These gels exhibit improved swelling in an acidic media, and low pH values favour the expansion of their chain dissociation. Vinyl pyridine, diethylamino ethyl methacrylate, aminoethyl methacrylate, and dimethyl aminoethyl methacrylate are a few examples of monomers employed in the creation of cationic hydrogels (Ramos et al. 2013). Anionic hydrogels, on the other hand, have a negatively charged backbone. Because these hydrogels dissolve more at higher pH, they swell better in neutral to basic liquids. Maleic acid, acrylic acid, itaconic acid, p-styrene sulphonic acid, crotonic acid, and methacrylic acid are anionic hydrogel monomers (Singhal and Gupta 2016). Ampholytic hydrogels, the third type of charge hydrogels, can have both positive and negative charges on one single polymer chain. Every structural repetitive unit in these hydrogels has both basic and acidic groups, and they are all balanced at an isoelectric point. These hydrogels' overall ionic characteristics can be altered by a small pH adjustment. A monomer for the creation of ampholytic hydrogels is N-isopropylacrylamide/ [[3- (methacryloylamino) propyl] dimethy (3-sulfopropyl) ammonium hydroxide] (Singhal and Gupta 2016).

Based on Cross-Linking

As hydrogels are mostly made up of cross-linking networks, they are divided into two types depending on cross-linking i.e., chemically crosslinked and physically

crosslinked or self-assembled hydrogels (Slaughter et al. 2009). The crosslinking process in physical gels is physically complex like hydrogen bonding, chain aggregation, crystallization, hydrophobic association, and polymer chain complexion (Ullah et al. 2015). To create a chemically crosslinked hydrogel, a chemical covalent crosslinking stage is used (either simultaneously with polymerization or post-polymerization). Chemical hydrogels are permanent and irreversible due to persistent configurational changes in the molecular structure, but physically crosslinked hydrogels are reversible due to modifications in conformation (Ullah et al. 2015).

Based on Methods of Preparation

Hydrogels are also classed on their fabrication/preparational methods, like (1) homopolymers, (2) copolymers, (3) semi-interpenetrating networks, and (4) interpenetrating networks (Fig. 1). Homopolymers are networks of polymers created from a single monomer and a fundamental structural component for a polymeric structure. It might have a crosslinked framework depending on the ingredient and polymerization technique. As a result of their responsiveness to outside stimuli, PEG-based hydrogels are frequently utilised in systems for drug delivery (Iizawa et al. 2007). Copolymeric hydrogels are composed of a pair of distinct kinds of monomer units, at least one of which is hydrophilic. To transport drugs, a biodegradable tri-block poly (ethylene glycol)-poly(-caprolactone)-poly (ethylene glycol) co-polymeric hydrogel can be used in this study (Gong et al. 2009). When a linear polymer penetrates a cross-linked structure lacking any other chemical interactions, it creates a semi-interpenetrating network. For example, semi-IPNs can better handle pH or temperature changes while providing benefits such as flexible pores and progressive drug release because there is no limiting interpenetrating elastic network. The retention of linear cationic polyallyl ammonium chloride in acrylamide/acrylic acid copolymer hydrogels, which increases mechanical strength and allows for fully reversible pH switching of theophylline release, is one illustration to support the situation (Zhang et al. 2009). By dipping a pre-polymerized hydrogel into a mixture of monomers and a polymerization catalyst, these networks develop. The presence of the permanent interlocking of network segments, allows the Interpenetrating network (IPN) to accomplish controlled phase separation and get around thermodynamic incompatibility. The integrity of both bulk and surface characteristics is thought to be ensured by the interlocking structure of the cross-linked IPN components (Maolin et al. 2000). IPNs are primarily described as the close union of two polymers in the presence of at least one being instantly synthesised in the presence of the other one (Ullah et al. 2015).

Advances in Hydrogels (Based on Stimuli)

Environmental-specific, intelligent hydrogels are hydrogels that react to external stimuli and undergo unanticipated alterations to their growth processes, the structure of networks, mechanical properties, and permeability (Gil and Hudson 2004). Chemical stimuli that change the interactions among polymeric chains and solvents as well as polymer networks at the molecular scale include the pH, ionic factors, and chemical substances. A biochemical stimulation responds to ligands, enzymes, antigens, and other biochemical agents. Damiri et al. (2022b) created glucose and pH-responsive hydrogels with chitosan and 4- 4-formylphenylboronic acid for the controlled release of insulin. Physical stimuli, which alter molecular level interactions at crucial points, include light, temperature, pressure, mechanical stress, magnetic and electric fields, and intensity of different energy sources (Ullah et al. 2015). Using UV light irradiation (PVA-MA), thermally sensitive poly(N-isopropyl acrylamide) PNIPAM was attached to the robust polymer backbone of poly (vinyl alcohol) (PVA) and its methacrylate derivatives. After the one-pot polymerization, the samples were submerged within a sodium sulphate salt solution to further strengthen the hydrogel network, where the PVA clumps and crystallises under these conditions (Pardeshi et al. 2022). Other than these basic parameters, hydrogels can also be classified as conventional and smart based on physical properties, and non-biodegradable, biodegradable hydrogels, depending upon the degradation pattern.

Properties of Hydrogels

Hydrogel has numerous properties which contribute to field applications. Polymer hydrogels are often fragile, soft, and brittle and are unable to sustain significant deformations. A hydrogel's structure and composition are crucial factors in determining its mechanical strength (Shibayama 2012). The medical and healthcare sectors can use hydrogels because of their mechanical properties, which include maintaining the physical texture of therapeutic ingredients during administration. This is important for biomedical applications like ligament and tendon repair, drug delivery matrix, dressing material for wounds, repair of tissue, and cartilage replacement material (Mishra et al. 2018). Future applications of the matrix of hydrogel in the drug, medical, eye disease, and tissue repair sectors will be characterized by its swelling properties (Zhang et al. 2020). Biodegradation is an essential component of biomedical applications, which calls for controlled absorption in vivo and targeted dispersion to support cell morphogenesis and motility. However, a variety of mechanisms (including the process of hydrolysis, the breakdown of proteins, disentanglement, or environmental

stimuli) could cause local or bulk breakdown of hydrogels; it is difficult to engineer the spatiotemporal aspects. Connecting massive hydrolytic dissolution to particular periodic occurrences within the human body, like the regeneration of bones, can improve the repair of tissues by regulating the amount of hydrolytically responsive linkages in the network of polymers (Seliktar 2012). Hydrogels can be used as tissue adhesives in surgical wound healing or as inductive scaffolds for the regeneration of tissue because of the significant property of bio adhesion, which also allows cells and tissues to attach to hydrogels. The majority of other naturally occurring and manufactured hydrogels do not have bio-adhesive qualities, even though some hydrogels, such as collagen or fibrin, do. Crosslinking molecules that permit covalent or non-covalent molecular connections between the implant and the surrounding environment, such as cell-adhesive oligopeptides generated from fibronectin's core cell-binding domains, can be used to build cell-adhesive characteristics into a hydrogel network (Censi et al. 2012). Hydrogels must be both toxic-free and compatible to be employed by the biomedical industry. To be employed for this purpose, the majority of polymeric substances have to undergo in-vivo toxicity tests. Biosafety and bio-functionality are two factors that go into a biocompatibility examination. The former indicates a sufficient host reaction, including both local and systemic (i.e., surrounding tissue) responses, as well as the lack of cytotoxicity, mutant development, and carcinogenesis, whereas the latter shows the material's ability to carry out the desired task (Dasgupta et al. 2013). Nowadays seeing the importance of proteins, these are utilized for hydrogel formation and have various biomedical and food applications. The following section provides a detailed explanation of proteins utilized for the preparation of hydrogels.

Protein Hydrogels

All organisms, from microorganisms to primates and larger animals, depend on proteins as key macromolecules. Protein can make up as much as 50% of the dry mass of some cells. The proteins connect to different biomolecules such as lipids, carbohydrates, phosphate bonds, DNA and metal ions by covalent or non-covalent interactions (Panahi and Baghban-Salehi 2019). DNA is the genetic blueprint for protein synthesis for a cell's genetic material and all living cells synthesize proteins using replication, transcription, and translation. The basic primary structure of a protein molecule consists of a linear sequence of polypeptides which may contain up to 20 different amino acids. These amino acids possess other functional groups that can be chemically modified (Whitford 2005). Several biomaterials, including hydrogels, films, and composites, have been developed (Ashfaq et al. 2022). Depending on their applications, hydrogels are manufactured in various shapes, including cubes, hollow tubes, rods, sheets, and films (Shi et al. 2014). According to Totosaus et al. (2002), protein-based hydrogels are made through (Table 1) enzymatic, chemical, or physical processes (heating, cooling, high pressure, etc.). The unfolding of the native protein structure and development of a gel network is the most significant process in the protein's gelation process. The constructed network can store water within its framework. Hydrophobic, electrostatic, and hydrogen bonding are examples of non-covalent cross-links that can keep these gel networks stable. Additionally, these could also be stabilized through covalent cross-linking (Le et al. 2017).

Animal Protein

The extracellular matrix contains collagen as a natural polymer. Around 30% of all the proteins in animals are made up of animal collagen, which is present in the dermis, bones, and articular tissues of animals. Collagen is primarily a fibrous protein, responsible for critical mechanical functions throughout the body (Gyles et al. 2017). Bone and cartilage contain high concentrations of collagen, which is essential to the structure and function of these tissues. Additionally, collagen can be used to connect and release cell regulators like cytokine and growth elements. Biomaterials such as collagen are frequently employed in tissue engineering (Cen et al. 2008) which is utilized both in its original fibrillar and in denatured state. The latter produces several collagen shapes, such as sheets, tablets, pellets, and sponges. In addition to its utility in tissue engineering, collagen has been utilized as a protein, medication, and gene delivery method (Aigner and Stöve 2003). Gelatin is created when collagen's triple-helix structure is broken down into single-strand molecules. There are two varieties of gelatin, types A and B. The former is produced after acidic pre-treatments of collagen and thermal decomposition, while the latter is produced after alkaline treatment. This process transforms glutamine and asparagine residues into glutamic and aspartic acids, yielding a greater concentration of carboxylic acid in gelatin B (Jonker et al. 2012). A simple temperature change is all it takes to gel a gelatin solution. Gels made from gelatin are non-immunogenic, biodegradable, and biocompatible; making them good candidates for use in biomedicine. On the other hand, these have poor thermal and mechanical stability. Chemical changes, such as cross-linking, improve the stability of these for long-term biological uses and several tissue engineering applications employ gelatin-based materials (Kuijpers et al. 2000). The ability of collagen-based hydrogels to replace or temporarily repair injured or diseased tissues makes them appealing for use in hemostasis devices and wound dressings (Doillon et al. 1997). However, the application possibilities for collagen-based hydrogels are constrained by their rapid in-vivo breakdown and low mechanical strength. Because of

Table 1 Hydrogel materials and their methods of production

Method of production	Materials	Key findings	References
Heat	Whey protein isolate and lotus root extract (LRA)	The gel strength of WPI gel containing 1% LRA was increased 12.5 folds compared to WPI alone.	Liu et al. 2017
	Thick egg whites and thin egg whites	Heat-induced gels made from TKEW and TNEW were studied and it was concluded that TNEW gels were hard and brittle TKEW gels soft and tough.	Liu et al. 2020a
	Soy protein and wheat bran cellulose (WBC)	Soy protein and WBC hydrogel was prepared by heat-induced gelation and it was found that gel strength and water-holding capacity were improved by WBC addition.	Xiao et al. 2020
	Pea protein isolate	Transglutaminase treatment was provided to heat-induced PPI gels and it was found that MTGase did not alter the thermal properties of the gel.	Shand et al. 2008
	Casein-κ-carrageenan	The presence of κ-carrageenan increased the thermal denaturation temperature of casein hydrogels.	Tang et al. 2019
Cold-set gelation	Whey protein	Flow behaviour of whey protein and whey protein-tara-gum gels was studied after giving magnesium chloride treatment	da Silva et al. 2010
	Pea protein isolate	PPI nanoparticles were prepared using calcium crosslinking for delivery of resveratrol with improved antioxidant ability.	Fan et al. 2020
	Soy protein	The effect of calcium sulphate-induced preaggregation of soy protein gels was studied and it was observed that as the calcium concentration increased, the gel became stiffer.	Wang et al. 2018
	Zein and casein	Zein and sodium caseinate nanoparticle dispersion was done by pH system for drug delivery.	Pan and Zhong 2016
Pressure	Bovine serum albumin (BSA) and gelatin	BSA-gelatin hydrogels were prepared by high pressure at 300 MPa for 15 min at 10 and 80 °C. While pressurization at 80 °C resulted in an inverse dispersion of BSA as the continuous phase supporting liquid gelatin inclusions, pressurization at 10 °C formed continuous gelatin networks with dispersed BSA inclusions.	Semasaka et al. 2019
	Soy protein	Folic acid-loaded soy protein/polysaccharide nanogels were prepared using high-pressure homogenization and folic acid remained structurally intact under all conditions until released.	Ding and Yao 2013

Table 1 (continued)

Method of production	Materials	Key findings	References
Enzymes	Whey protein	Whey protein was treated with MTGase and the denaturation temperature (Td) of -lactoglobulin in WPI was dramatically raised by the MTGase treatment, rising from 71.84 °C in the sample without treatment to 78.50 °C after 30 h.	Agyare and Damodaran 2010
	Casein	Gels of sodium caseinate (15% w/w), transglutaminase cross-linked expanded in good solvents or shrank in bad solvents until an equilibrium casein volume fraction was attained,	de Kruif et al. 2015
	Soy protein	Transglutaminase crosslinked soy protein emulsion gels having different compositions and content of oil showed different textural and microstructural properties.	Zhang et al. 2020
	Gelatin-alginate	Microspheres composed of alginate and gelation crosslinked by transglutaminase and calcium chloride were developed with higher water content.	Pilipenko et al. 2019

this, recent research has concentrated on developing composite hydrogels that incorporate collagen composites with other polymers that have improved mechanical strength and degradation (Sahiner et al. 2014). It is possible to create collagen-based hydrogels by physical processes. The reforming of fibrils and the formation of a hydrogel network is caused by the aggregation of collagen through covalent bonding, which is initiated by heating and an increase in pH. However, collagen in real tissues forms inter and intramolecular covalent connections via hydroxylysine as well as lysine residues, these hydrogels are weak in terms of their mechanical strength wherein additional cross-linking is often regarded as the most effective strategy for overcoming this hindrance (Antoine et al. 2014). Similarly, these were additionally cross-linked with gamma radiation, carbodiimide, genipin, glutaraldehyde, and these substances. Several compounds were used to synthesize standard, hybrid or composite collagen hydrogels to modify the properties of conventional hydrogels (Chen et al. 2016).

The majority of the cytoplasmic epithelium and the outermost layer of the epidermis is made of the fibrous protein group keratin, which is abundant in animal hair, fingernails, fibres such as wool, horns, and feathers—all of which contain over 90 per cent by weight. These products can be used in a wide range of industrial settings. It can be divided into two categories: hard keratin and soft keratin. The stratum corneum layer in the skin, which is an example of epidermal keratin, is known as soft keratin and includes 1% sulphur, whereas the latter is found in strands of hair nails, horns, and feathers and has about 5% sulphur. The high cysteine content of the hard keratin gives it greater durability and structural stability (Shavandi et al. 2017). Keratin-based materials, in contrast to collagen-based ones, are mechanically strong and biodegradable in vivo. As a result, it can be used to build scaffolds for permanent cell culture. For example, keratin-based hydrogels have drawn a lot of interest in the discipline of peripheral regeneration of nerves. In this instance, keratin-based hydrogels can be introduced inside a nerve channel as a filler to direct nerve regeneration. Regenerative scaffolds and injectable drug delivery devices are two more uses for keratin-based hydrogels (Rouse & Van-Dyke 2010). The keratin needs to be first cross-linked, either chemically or by the formation of disulfide bonds, to produce these hydrogels. For instance, to hasten the formation of these bonds, the keratin solution could be combined with a hydrogen peroxide solution. The combination that results is then incubated for an additional day to create a gel. In a different study, both potassium persulfate, as well as sodium bisulfite, were added to a solution of hydrolyzed feather keratin as initiators. (Wattie et al. 2018).

Milk Protein

Casein, the most abundant protein in milk, includes approximately 94 per cent of protein combined with colloidal calcium phosphate. Milk-based hydrogels can also be made with casein (proline-rich open-structured phosphoproteins from milk) only or it can be combined with other food-grade polymers. Caseins may self-assemble or aggregate into various protein structures (Dickinson 2006) and are sensitive to pH fluctuations. It is generally insoluble, however, becomes solubilized above pH 5.5 and below pH 3.5, while

it is insoluble between 4.5 and 5.0 pH (Nascimento et al. 2020). In addition to other positive traits like biocompatible, non-toxic, and reactive sites are available for alteration, caseins, & casein derivatives contain a majority of hydrophilic functional groups, such as lysine and glutamine residues, which may impart significant functional attributes to the hydrogel (Gorji et al. 2014). The addition of chemicals such as crosslinking agents can generate a variety of casein-based hydrogels wherein the amount of agent makes a profound impact (Song et al. 2009). Casein hydrogels can also be made via enzymatic cross-linking. To gel the milk proteins, enzymes such as transglutaminase could be utilized at relatively mild conditions resulting in a hydrogel suitable for biomedical applications (Elzoghby et al. 2011).

The remaining milk proteins constituting whey proteins have many beneficial features, including highly functional, biological, and nutritional. Whey protein's primary constituents are globular proteins, such as lactoglobulin and lactalbumin. For the creation of protein-based hydrogels, numerous studies have documented the use of whey protein products, particularly whey protein concentrate and isolate, or other whey constituents (especially lactoglobulin and bovine serum albumin), to encapsulate and distribute bioactive molecules and micronutrients (Deeth and Bansal 2019). Therefore, cold set hydrogel-forming properties of whey proteins are well-known wherein acidulating agents like glucono-d-lactone (GDL) or salt-induced cold gelation are used to create soluble aggregates through a two-step process that begins with heating and culminates with cooling (acid-induced cold gelation) (Brodkorb et al. 2016). Hydrogels produced by the cold-set gelation method are capable of providing efficient delivery of heat-sensitive nutraceutical ingredients like vitamins and probiotics better than heat-set gels can. More recently, Alavi et al. (2018) created a new gelation technique based on radical protein cross-linking, doing away with the heating stage and causing non-heated whey proteins to gel. whey protein-based hydrogels created by cold-set gelation technique are expected to have poor mechanical strength, which makes them susceptible to enzyme degradation.

Plant Protein

Plant proteins are receiving more attention in the food industry as a result of consumers' growing concerns about the safety of products made from animal products and their evolving dietary habits and culinary preferences. Being unstable at around their isoelectric point, these proteins do not function well in acidic pH conditions (Hertzler et al. 2020). Corn (also known as maize) is one of the most extensively produced crops on the planet. In addition to proteins like glutelin, globulins, and albumins, zein is a vital storage protein present in the endosperm of maize kernels. In maize kernels, it accounts for 44–79 per cent of the total protein content (on a wet basis) (Shukla and Cheryan 2001). The significant percentage of non-polar amino acids in nature (about 55%) makes it a hydrophobic protein. Zein has a regular geometry and is amphiphilic, which allows it to assemble itself into chains, sections, or foam by various processing techniques. It is possible to encourage the controlled aggregation of zein protein molecules, which results in a zein layer, on a surface that is hydrophobic (such as metal, glass slides, or manufactured polymer). This aggregation tendency is caused by the link between the hydrophobic groups of zein and the hydrophobic region (Dong et al. 2013). Zein protein molecules remain to form aggregates on a hydrophobic surface after that, eventually forming a film layer or a gel structure. Zein's ability to self-assemble into a variety of microstructures, such as films and fibres, is a result of its amphiphilic nature. Because of its one-of-a-kind quality, it is possible to synthesize materials (hydrogels) that have the potential to be used in several areas, particularly in the encapsulation of drugs and controlled drug delivery (Sousa et al. 2012).

Soy protein is a significant by-product of the soybean oil industry. Owing to its excellent nutritional content, emulsifying capacities, and gel formation properties, it bestows good functional properties for food preparation. Soy protein has an isoelectric point of pH 4.8, which is the prime reason for its limited applications in most foods that are acidic in nature. Typically, soybean comprises 15–25 per cent oil, 35–45 per cent protein, 33–35 per cent carbohydrate (soluble and insoluble), and 5–6 per cent ash on a dry basis (Liu et al. 1997). It is distinguished by its propensity for forming gel and foam, which is crucial for creating porous hydrogels. These porous hydrogels are useful for the development of tissues, nutrient transportation, and the creation of hygienic products because they feature large and interconnected pores, a larger surface domain, and an excellent swelling rate (Kang et al. 2005) (Santin and Ambrosio 2008).

Furthermore, hydrogels made from soy protein have significant applications in controlled compound release, orthopaedic implants, and superabsorbent materials (Zohuriaan-Mehr et al. 2009). Soy proteins can gel by a variety of methods, including heat gelation, cold setting gelation, chemical and enzymatic crosslinking, and others. Because of the unfolding and exposing of hydrophobic areas following thermal treatment, soy protein molecules can interact and combine to produce stable hydrogels (Puppo and Anon 1998). Another method of gelation, known as the cold gelation process, globular protein mixture (heat-denatured) after inducing gelation at room temperature by reducing pH or adding calcium is created. The quantities of soy and calcium used determine the properties of the resultant hydrogel (Alting et al. 2002). For example, a larger protein concentration can enhance the gel's ability to hold water, whereas

a higher $CaCl_2$ (calcium chloride) concentration can raise the gel's opacity and elastic modulus. But soy hydrogels created through thermal gelation or cold gelation are weak mechanically and lose their strength soon. Enzymatic or chemical crosslinking can be used to improve this (Maltais et al. 2005). The removal of toxic substances from industrial effluents is one potential application of hydrogels made of soy. To create hydrogels with greater stability and cellular affinities, soy protein isolate (SPI) is also combined with collagen, zein, and other proteins. To get the appropriate hydrogel characteristics and reduce the amount of soy protein contaminants, extraction conditions should be optimised for usage as biomaterials (Panahi and Baghban-Salehi 2019).

Composite Hydrogels

Hydrogels made from natural biomaterials or synthetic polymers cannot accurately duplicate all of the characteristics of the original extracellular matrix for tissue engineering and offer some disadvantages in other food and biomedical applications because of the inherent limitations of both types of hydrogels. Hydrogels comprise both synthetic and natural components. Combining the advantages of both synthetic and natural polymers (for example, cell-adhesive compounds and fibrous structure) will result in a composite hydrogel (Afewerki et al. 2019). Furthermore, naturally generated polymers, which include collagen and gelatin, are prone to change from batch to batch, have subpar mechanical properties, and have a low level of biochemical stability (Pradhan et al. 2016). Several studies (Chen et al. 2015; Nonoyama et al. 2016; Zhang et al. 2016) addressed the functions and advantages of double networks or interpenetrating networks made of natural-natural, synthetic-natural, and synthetic-synthetic hydrogels. Marine-derived collagen and agarose were recently added to alginate in an investigation including bioactive gel for 3-D cell culturing to develop a physically crosslinked hydrogel. With a range of cell types, this composite hydrogel showed outstanding cytocompatibility. The multicellular structures that developed within this composite hydrogel were what produced exceptional yields (Shin et al. 2016).

Furthermore, polysaccharides can be combined with gelatin to increase their bioactivity (Afewerki et al. 2019). Due to its antibacterial qualities, biocompatibility, and biodegradability, chitosan is a desired polysaccharide (Mohanty et al. 2018), although can be improved by adding gelatin because it has poor bioactivity and sluggish gelation. At pH 6.5, positively charged chitosan can combine with gelatin (negatively charged) to produce polyelectrolyte complexes. The bioprinting of a structure used a mixture of alginate and gelatin as bio-ink. This printed construct's mechanical characteristics were comparable with those of pre-crosslinked alginate, but it was superior in promoting cell growth (Chung et al. 2013). Li et al. (2021) investigated the gels of the sodium alginate (Alg)/casein composite produced by glucono-d-lactone (GDL) and their physical characteristics. The results showed that as the Alg concentration increased, the gel hardness initially increased but then decreased, corresponding to the structural transition of the composite gels. The gels had 8.0 per cent, w/v casein concentration and 0–1.0 per cent, w/v Alg concentration. At low Alg concentrations (0.1 per cent), the composite gel had a casein-dominant network; however, when Alg concentrations rose (e.g., 0.2–0.5 per cent), the caseins took over as the continuous gelling phase and the Alg served as the dispersed phase. Wei et al. (2016) studied the correlation of structure and pH in sodium caseinate (SC) and N, O-carboxymethyl chitosan (NOCC) based composite hydrogel. According to rheological experiments, the optimal hydrogel ratio was SC/NOCC = weight ratio 3/7. AFM confirmed the well-developed three-dimensional network structure of hydrogel. The resultant hydrogel also exhibited outstanding pH sensitivity. Temperature variations had a significant impact on the gelation process; a high temperature led to an earlier start to gelation.

Methods for the Preparation of Protein Hydrogels

Heat-Induced Hydrogels

When protein solutions are heated, the unfolding and disruption of protein molecules are triggered, leading to the exposure of hydrophobic groups and the creation of disulfide bonds. In conclusion, the production of heat-set gels is caused by the association of the unfolded protein molecules and the involvement of intermolecular-sheet topologies (Oztop et al. 2014). A network is generated in whey protein heat-induced gels which include hydrogen bonds, hydrophobic and ionic interactions, along with covalent (intermolecular-and intramolecular disulfide bonding) and non-covalent (ionic and hydrophobic) interactions (Oztop et al. 2014). The whey protein isolate (WPI) and lotus root amylopectin (LRA) composite gels were made utilising a similar heat-induced method and possessed high values for the strength of the gel, capacity for holding water, storage modulus, and better rheological properties (Liu et al. 2017). LRA was heated to 80 °C in this method after being kept for 12 h at 4 °C. After that, to stabilise the matrix within the WPI-LRA composite hydrogels, the LRA solution was combined with the WPI solution and heated at 95 °C for 30 min in a water bath. Using cellulose nanocrystals that were derived from wheat bran, Xiao et al. (2020) improved the characteristics of heat-induced whey protein gels to create a hybrid gel with a compressed and stable structure. By

using the heat-induced approach, Liu et al. (2020a) investigated the gel characteristics and microstructure by comparing thick egg whites (TKEW) and thin egg whites (TNEW). The results showed that the heat denaturation temperature of TKEW was greater than that of TNEW (72.51 °C). In addition, the heat-induced approach was used to examine the rheological characteristics of hydrogels made from pea protein isolate (PPI) using microbial transglutaminase (MTGase) as a crosslinking agent (Shand et al. 2008). After heating the PPI hydrogel at 92 °C, MTGase was added and incubated at 4 and 50 °C, respectively. The results demonstrated that PPI gels incubated at 4 °C had higher shear stress and strain than those at 50 °C. To sum up, the temperature of heating and the heating time frame are two crucial factors that affect the structure, characteristics, uses, and applications of hydrogels in heat-induced hydrogels.

Cold-Set Induced Hydrogels

Whenever the protein-containing liquid undergoes heating at a neutral pH level (above the isoelectric point), beneath the protein gelling extent, and with low ionic strength, the initial step of cold-set gel formation starts in globular food proteins, leading to denaturation and partial unfolding of proteins (Abaee et al. 2017). The next step is either salt supplementation (mono, di, and multivalent cations) (salt-induced cold gelation) or acidification to reach the protein's isoelectric pH to reduce inter-protein repulsion and create cross-linkages (divalent and multivalent cations) between clusters of proteins (Kuhn et al. 2010). A study showed how globular proteins can be cold-gelled using calcium chloride and sodium chloride (Kuhn et al. 2011). To create whey protein-based cold-set gels with increased nutritional value and functioning, other cations, such as iron and magnesium (divalent), have also been used (da Silva et al. 2010). One of the primary benefits of cold-induced gel formation over other techniques is the ability to interact bioactive ingredients with polypeptide chains through a variety of interactions that include hydrogen bonding, electrostatic force, and hydrophobic interactions due to exposure to various functional groups inside protein molecules. According to Abaee et al. (2017), targeted delivery systems can be developed through these newly established connections between bioactive chemicals and proteins. Additionally, the cold-induced method gives the final shape, structure, and texture of the generated gel (Egan et al. 2014).

Pressure-Induced Hydrogels

Food proteins can also be gelated via high-pressure processing, a unique method demonstrated by several workers. Proteins are denatured by high-pressure processing by rupturing electrostatic and hydrophobic interactions. In comparison to the heat-induced gelation approach, it has been suggested to offer fewer advantages because it solely affects the breaking of hydrogen bonds (Ngarize et al. 2005). These advantages include the production of a softer and smoother texture as well as the prevention of browning reactions (Apichartsrangkoon 2003). In a study by Semasaka et al. (2019), bovine serum albumin, also known as BSA, and gelatin were combined to form a composite hydrogel at 10 and 80 °C for 15 min, respectively. The findings showed that at 10 °C, a continuous gelatin network structure with dispersed BSA inclusions existed, whereas, at 80 °C, an uninterrupted BSA reversed dispersion phase with supportive gelatin inclusions existed. The unique characteristic of the gelatinization of starch procedure carried on alternatively by extreme pressure or heat was also revealed by Liu et al. (2020a). They discovered that starch was gelatinized in different ways as a result of high pressure and heat. High temperature-induced the gelatinization process selectively disrupted unstable crystallites whereas high pressure-induced the gelatinization process disturbed crystallites of all stabilities. Hydrogel structure and gelation properties were mainly studied using high-pressure processing. However, for use as a delivery mechanism for bioactive components, this hydrogel production process will need to be improved significantly in the future.

Enzyme-Induced Hydrogels

Enzymatically crosslinked hydrogels have been receiving a growing amount of attention for a few decades. The majority of enzymes are capable of catalyzing reactions that are enzymatic at neutral pH, in an aqueous environment, and at mild temperatures, suggesting that they can be used to create in situ hydrogels (Teixeira et al. 2012). Due to one of the best qualities of this sort of reaction, undesirable side reactions or toxicity could happen while employing photo-initiator compounds or organic solvent compounds. Also, enzymes specifically target a substrate (Davachi et al. 2022). Because of the relatively mild form of the enzyme-mediated processes that occur under typical physiological settings, this emphasises the benefit of this technique in interconnecting organic polymers, which are unable to endure strong chemical conditions. Therefore, any potential loss of bioactivity is avoided as a result. Sofia et al. (2002) found that modulation of enzyme activity can directly regulate the polymerization reaction. Thiol enzymes called transglutaminases to catalyse post-translational protein modification, mostly by causing the formation of isopeptide bonds, but also by covalently conjugating polyamines, esterifying lipids, and deaminating glutamine residues (Krishna and Wold 1998). Transglutaminases catalyse the production of covalent connections between the amino acid glutamine (peptide-bound) or carboxylic group and the free amine group of the protein,

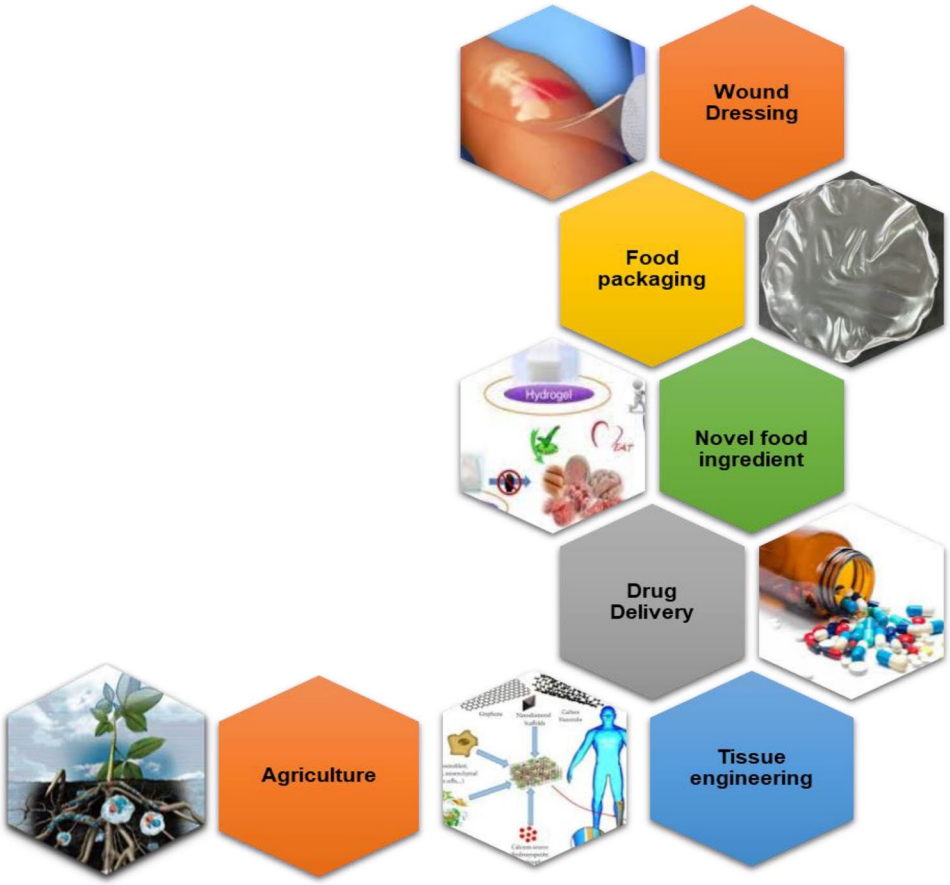


Fig. 2 Layout of potential applications of hydrogels in various fields

serving as a substitute for chemical crosslinking. These connections are highly resistant to proteolytic breakdown once they have been established. As a result, co-factors are not required to create stable polymeric networks (Teixeira et al. 2012). Fish protein (Li et al. 2019), whey protein (Agyare and Damodaran 2010), casein (Duerasch et al. 2018), gelatin (Pilipenko et al. 2019), soy protein (Zhang et al. 2020), and chitosan have all been used as a result of transglutaminase in recent years (Jiang et al. 2016).

Applications of Protein Hydrogels

Hydrogel has several applications in various fields, (Fig. 2; Table 2) and under this section, applications in biomedical sectors, food sectors and agriculture sectors are covered.

Biomedical Sector

Hydrogels, nanofibers, hydrogel nanofibers, foam and spongy, bilayered, and trilayered scaffolds are some of the biomaterials being created and studied to hasten the healing of chronic wounds (Ijaola et al. 2022). Hydrogels composed of gelatin and hyaluronic acid (HA) which have been cross-linked in different ratios have been studied for wound healing using both vivo and in vitro wound repair models to evaluate their effectiveness. environmentally friendly gelatin/hyaluronic acid hydrogels may be useful as wound dressings due to enhanced cell growth in vitro compared to controls and wound healing in vivo (Wu et al. 2017). In situ-forming gelatin and oxidised alginate, hydrogels were the subject of another study as potential wound-healing material. The findings showed that a modest amount of borax caused periodate oxidised alginate to quickly cross-link the hydrogel's proteins, causing gelatin to cross-link in the wound. (Balakrishnan et al. 2005). Additionally, keratin from discarded human hair or wool was employed to create hydrogels that were then cross-linked using an electron beam in a mixture of polyvinyl alcohol (PVA) and polyethylene imine. Compared to the control group (blank or hydrocolloid wound dressings), injuries that received keratin-based hydrogel dressings closed more quickly, most likely as a result of the creation of new collagen (Park et al. 2015). Electro-spun nanofibrous mats made of casein and PVA successfully promoted haemostasis by generating thrombin whereas increased epithelial proliferation and restoration were achieved by adding casein (Biranje et al. 2019). Additionally, wound healing has been aided by developing casein/

Table 2 Applications of protein-based hydrogel

Applications	Materials	Key Findings	References
Wound healing	Gelatin/ hyaluronic acid	Gelatin-hyaluronic acid (8:2) dressings had good water vapour transmission rate, rate of water evaporation and moisture-holding ability, for wound healing.	Wu et al. 2017
	Gelatin/Alginate	The hydrogel formed by gelatin-alginate could uptake 90% of water and provide a moist environment for wound healing.	Balakrishnan et al. 2005
	Keratin, PVA and polyethylene imine	It was demonstrated that keratin-based hydrogels speed up the healing of excision wounds by boosting the production of collagen.	Park et al. 2015
	Casein and PVA	It was shown that an electro-spun casein/PVA nanofibrous matrix can successfully increase bioactivity and be helpful for the creation of hydroxyapatite by simulating the natural biomineralization of bone.	Biranje et al. 2019
Tissue engineering	Alginate/gelatin	The hydrogel nanofiber formed using alginate and gelation had low cytotoxicity and enabled the maturation of human iPSC-derived ventricular cardiomyocytes and an over 8-fold proliferation of mesenchymal stem cells over the course of 5 weeks.	Majidi et al. 2018
	Collagen	Here collagen-based hydrogel nanofibers were developed and were successfully able to mimic the human extracellular matrix (ECM).	Wakuda et al. 2018
Drug delivery	Casein	It was demonstrated that casein hydrogel formed using genipin was suitable for entrapment and better release of bovine serum albumin (BSA) at pH 7.4.	Song et al. 2009
Probiotic delivery	Whey protein and alginate	Alginate-whey protein concentrate and alginate-whey protein hydrogel showed more cell release for probiotics, indicating that whey protein combined with alginate offers an improved porosity and physically stronger matrix than alginate beads alone.	Krunić et al. 2019
	Soy protein	The research's findings demonstrated that soy protein is a workable substrate for creating probiotic microparticles that dramatically increase both bacterial survival and tolerance to simulated gastrointestinal fluids.	González et al. 2018
Food packaging	Collagen, agar and alginate	Collagen/agar/alginate blend hydrogel films were incorporated with silver nanoparticles and used as a packaging material (antimicrobial and antifogging) for potatoes to keep them fresh.	Wang and Rhim 2015
Encapsulation	Caseinate and methoxyl-pectin	Fish oil encapsulated in caseinate-methoxyl-pectin hydrogel microspheres had improved stability for lipid oxidation.	Zhang et al. 2014
Polyphenol delivery	Pea protein isolate (PPI)	PPI nanoparticles were prepared using calcium crosslinking for delivery of resveratrol with improved antioxidant ability.	Fan et al. 2020
	Gelatin	The gelatin-based hydrogel was prepared using genipin as a crosslinker for the release of vitamin B6.	Teimouri et al. 2019
Vitamin delivery	Milk protein, sodium caseinate	Vitamin A with improved stability was delivered with the help of milk protein complexes.	Gupta et al. 2017

Table 2 (continued)

Applications	Materials	Key Findings	References
Carotenoids delivery	Rice starch -whey protein isolate	Beta-carotene bioaccessibility was compared between emulsions, hydrogels and filled hydrogels and was found to be more in filled hydrogels.	Mun et al. 2015
	Zein-oligochitosan	Encapsulation of astaxanthin was done in the zein-oligochitosan complex having improved UV-light and storage stabilities.	Jiang and Zhu 2019
Fat replacers	Protein and dietary fibers	Hydrogel particles were formed using gelatin and pectin to mimic starch granules.	Wu et al. 2014
Agriculture	Whey protein (WP) and alginic acid (AA)	By utilizing WP and AA hydrogels were created by calcium chloride as a crosslinking agent for the sustained release of urea fertilizer in the crop.	Di Martino et al. 2021

cellulose/chitosan scaffolds. Nucleation sites for blood clotting ions were revealed by the presence of casein, which was needed for haemostasis (Biranje et al. 2022). Hydrogels made from casein and alginates are being investigated for use in intravenous injection and can be used in wound treatment owing to their porous nature, helpful in improving cell survival (Patwa et al. 2020).

Hydrogels featuring a three-dimensional could be employed in tissue engineering, and have proven to be very promising materials. They are qualified as potential candidates for implementation in tissue engineering techniques because they can mimic the physico-chemical characteristics of the original ECM, or extracellular matrix, (Lee and Mooney 2001). Gelatin and alginate hydrogel nanofibers discussed by Majidi et al. (2018) showed increased adhesion of cells, mobility, growth, and development, suggesting they can be useful in the treatment of stem cells and regeneration of tissues. An anisotropic collagen hydrogel nanofiber was created by Wakuda et al. (2018) wherein researchers employed a core-shell electrospinning process to meet the objective. It is vital to have anisotropy to closely approximate ECM, as a result of which the hydrogel nanofiber system finds applicability in tissue engineering scaffolds.

Numerous ways to deliver drugs (DDS) have been developed to meet the challenge of polypeptide and protein drug delivery (McClements 2017). Three-dimensional water-swollen polymeric structures are known as hydrogels. These types of DDS are created when polymeric chains interact physically or chemically. Due to their significant amount of water, they are utilised to administer a variety of drugs and biologically active substances (Khodaverdi et al. 2017). They offer several characteristics that make them ideal for medication delivery: (a) the ability to manufacture microparticles, nanoparticles, and films in various physical shapes. (b) Their permeability facilitates the controlled release of drugs for smaller molecules or macromolecules across the hydrogel network and provides an ideal atmosphere for the incorporation of drugs into the gel structure. (c) These include basic formulations, which allow for high local concentrations of encapsulated medications to stay in the tissues over time. (d) These are also quite biocompatible, which makes them perfect for application in vivo (Hoare and Kohane 2008). Natural hydrogels based on proteins, including gelatin, collagen, casein, and albumin, have been extensively studied and are regarded as an important DDS class (Elzoghby et al. 2011). Bovine milk's primary ingredient, casein, is widely available, reasonably priced, and possesses several fascinating fundamental and physicochemical characteristics, such as hydrophilicity and the availability of reaction sites for later modification, which make it an appealing option for novel DDS (Song et al. 2009). Various innovative DDS based on casein have recently been produced and successfully used, including self-assembled nanostructures, nanocomposite-based films, crosslinked casein micellar compounds, and hydrogels. Another significant attribute of a hydrogel is its ability to store water, and it has been discovered that casein hydrogel has a lower tendency to swell (Kruif et al. 2015). Based on such findings, casein appears to be a suitable material for building biocompatible polymeric hydrogels for delivering labile molecules like peptides and proteins. Chitosan-based freeze-dried hydrogels for the delivery of drugs including caffeine, ascorbic acid, and 5-fluorouracil (5-FU) were developed. Results depicted that chitosan can be used for in-situ target therapy (Damiri et al. 2020). Also, a similar study using chitosan and magnetite nanoparticles was conducted by Fouad et al. (2020). Hydrogel-forming microneedles are another smart approach for the transdermal delivery of drugs. The drug is delivered via a topical route using the microneedle delivery system by momentarily disturbing the skin's surface layer, which follows the diffusion mechanism. On a tiny patch, an array of hundreds of microneedles is organized to help distribute enough medication to have a therapeutic impact.

Food Sector

There are several uses for hydrogels in the food business, including food packaging and acting as transporters for bioactive components. Hydrogels can offer antimicrobial benefits and control the humidity produced by the food when used in packaging materials. This makes it possible to create smart packaging that enhances the quality, protection, and potential of food to be preserved for a long time (Shewan and Stokes 2013). To prepare packaging films for fresh potatoes, films containing a mixture of agar, collagen and alginate as well as antimicrobial ingredients like nanoparticles of silver and extract of seeds from grapefruit were mixed (Wang and Rhim 2015). The water absorption capacity of the finished film was found to be 23.6 per cent higher than its weight. In addition, the film demonstrated potent antibacterial action against the strain of Listeria monocytogenes (gram-positive) and the strain of Escherichia coli (gram-negative), both species are known to cause illness in humans. Caseinate and methoxyl pectin were complexed by electrostatic force by Zhang et al. (2014) to produce hydrogel microspheres that contained fish oil. First, a caseinate-based emulsion made from oil in water was created at pH 7 utilising caseinate as the emulsifier. Pectin was then added after the solution had been pH-adjusted to 4.5. Finally, to increase the long-term stability of the hydrogel matrix, the transglutaminase enzyme was employed as a cross-linking agent. Due to the encapsulation, which prohibited the polyunsaturated fatty acids (PUFA) from becoming oxidised, this showed the possibility of such hydrogel particles for delivering PUFA lipids in foods and beverages. At the same time, it does not affect their digestion in a small intestine model.

In addition, another important variable determining the quality of food products is how food is perceived to have been prepared. Hydrogel, a soft material, has many textural qualities (elasticity, hardness, chewiness, etc.). As a result, hydrogels can be utilised to enhance the texture and mouthfeel of foods in addition to substituting food components to reduce calorie consumption. For instance, emulsion hydrogels can change the textural properties of food (Devezeaux et al. 2016). It is interesting to note that a successful strategy for cutting calories in food is to substitute calorie-dense ingredients like meat or grain with calorie-light alternatives like hydrogels with excellent textural qualities or low oil content (Guo et al. 2013).

Due to the three-dimensional porous networks, the hydrogel is the perfect encapsulating option for water-soluble components, which may retain as much as several thousand times their dry mass. Hydrogels have been extensively used in the food industry as encapsulation solutions throughout the past few decades (Zhang et al. 2016). In contrast to the situation in the food business, the medical industry has conducted a large number of studies on the usage of hydrogels in encapsulation. Structurally, nanogels, hydrogels with core-shell structures, emulsified hydrogels, microgels and hydrogel nanomaterials are all structurally suitable for use as encapsulation platforms. Both the research on utilizing hydrogels for encapsulation and the research on using hydrogels for immobilization (of enzymes, cells, microorganisms, and so on) share certain parallels, although, some differences exist (Facin et al. 2015).

On the one hand, while immobilisation can occur within the hydrogel matrix or on its surface, encapsulation almost typically occurs exclusively within the network of the hydrogel. Additionally, since hydrogels are a three-dimensional network of interconnected pores, both the exterior and interior structural characteristics of hydrogels have a significant impact on their ability to immobilise (Lim et al. 2019). An extremely permeable hydrogel with a high or even super high absorption capacity may attract more attention from the general population, visualizing an immediate demand for developing products with decreased amounts of fat or starch. Hydrogels can be an effective tool in calorie reduction, either by increasing satiety or decreasing intake (Cao and Mezzenga 2020). Using proteins and fibre from food as light material approaches, Wu et al. (2014) produced hydrogel particles that had an excellent texture, that might serve as a more nutritious substitute for starchy flakes.

Enhancement of Nutrient Absorption and Digestibility of Hydrogels

Proteins are commonly employed in producing hydrogels due to their technological properties, which allow them to be used in various culinary products. Dietary matrices and digestive environments influence proteins because they are altered by pH, ionic strength, and proteolysis (Ozel et al. 2018). In the passage through the GIT (gastrointestinal tract), protein hydrogels can swell significantly under stomach conditions (Hashemi et al. 2017). Proteins with a pKa of 5 or below, may be associated with swelling during the gastric phase owing to the positive charges under the stomach's conditions, allowing the easy entry of water. However, it might be challenging to identify the cause of protein-gel disintegration, since it involves enzymatic activity and structural modifications that cause gel collapse. The gel protein in GIT's gel can have its swelling and breaking properties adjusted by chemical cross-linking or heat-induced aggregation (Okuro et al. 2021).

Additionally, since chemicals used to make polysaccharide hydrogels primarily do not react to enzymatic action, other chemical and physical changes within the GIT specifically stimulate modification (e.g. ionic strength, pH, shrinking and mechanical properties, swelling,). Gellan gum, alginate, pectin, and carrageenan are examples of anionic biopolymers that include carboxylic or sulphate groups,

making them particularly susceptible to the medium's pH and ionic strength (Okuro et al. 2021). Thus, the change in molecular conformation of these polysaccharides (which takes place during the passage through the GIT) can impact the macroscale and features associated with gels (Santos and Cunha 2018).

Agricultural Sector

Hydrogels have some potential applications in agriculture, which include the transport and precise distribution of minerals or agricultural fertilizing agents, the efficient use of wait and soil minerals, and the ability to provide desirable characteristics to agronomic goods without jeopardizing the ecosystem or its natural assets (Guilherme et al. 2015). The availability of moisture in the grounds allows for the supply of nutrients to vegetation that is essential for their growth. Even in dry soils, improving the environment for plant growth by increasing the amount of lost water is a benefactor. Hydrogels with superabsorbent properties can take in a substantial amount of water while maintaining their original size and weight. By decreasing the need for irrigation and the soil's propensity towards compaction, putting a stop to erosion and water run-off, boosting soil aeration and microbial activity, and so on, the use of these materials in agriculture could help to alleviate some of the issues that plague the agricultural industry (Rudzinski et al. 2002). Numerous potential uses for hydrogels exist in the area of water treatment, including the elimination of hazardous metals to be used further for irrigation purposes. Functional groups including sulfonic acid, carboxylic acid, amidoxime, amines, the hydroxyl group, and many more may function as chelating compounds for association with metallic ions present in these materials (Ekebafe et al. 2011). Protein hydrogels can play several significant roles in agriculture that improve crop productivity, soil health, and sustainability as a whole. The study that follows shows how protein hydrogels are used in agriculture. Da Martino et al. (2021) utilised whey protein and different concentrations of alginic acid for hydrogel preparation to retain soil moisture and efficient release of urea.

Conclusion

According to the findings of this review, proteins, and more specifically food proteins are a great candidate for smart as well as composite hydrogels that are capable of releasing biological molecules in a variety of circumstances due to their intrinsic properties. Bioactive substances can be made more stable and bioavailable with the help of a food hydrogel based on a protein which could be an excellent candidate to cater to the requirement. Hydrogels based on proteins have numerous uses in the biomaterials, drug, and food industries. Even though food protein hydrogels have already been widely employed and researched as bioactive ingredient delivery methods, some major scientific issues still need to be addressed for wider practical applications. Due to their water absorption and swelling properties, these hydrogels are ideal for encapsulating specific molecules and releasing them under controlled conditions. A growing number of studies have been published in scholarly journals regarding the structure of hydrogel prepared from milk proteins. Food hydrogel's interactions with the body are still unresolved and understudied scientific questions. This shows the wide range of possibilities that can be found in this subject of study. More inputs are required to further understand the structural features of protein-based hydrogels and discover industrial applications for these soft materials.

On the other hand, in terms of protein delivery approaches, hydrogels have several limitations, including irregular tissue formation, lack of spatial dissemination, cell dissociation and breakdown of proteins. Researchers should address the challenges associated with obtaining tailor-made drug releases and close the discrepancy between preliminary trials and results from clinical investigations. In the near times, studies must take into consideration the particular characteristics of the target tissues the attributes of Protein-based Hydrogels (PBHs) and their level of sensitivity in the target tissue. It carries immense importance in the field of protein characterisation leading to the importance of understanding the protein's structure, the advantageous associations among protein molecules and the matrix of polymers inside hydrogels, distribution strategies, and taking into account the importance of essential properties like biological compatibility. The potential to address complicated problems in healthcare, biotechnology, and other areas becomes more and more clear as research in this area develops. The scientific community may further unlock the incredible potential of protein-based hydrogels and lead humanity into an era of transformative applications by accepting the recommendations for future research areas.

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Declarations

Conflict of interest The authors declare no competing interests.

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