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Review Article

Keratin in drug delivery: A narrative review of sources, processing techniques, formulation strategies, and biomedical applications

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Abstract

Keratin is a naturally occurring fibrous structural protein that has attracted considerable attention as a biomaterial due to its excellent biocompatibility, biodegradability, low immunogenicity, and intrinsic cell-binding properties. These characteristics designate keratin as a promising candidate for biomedical and pharmaceutical applications, particularly in drug delivery systems. This study investigated keratin molecule, physicochemical properties suitable for drug delivery, some keratin-based formulations from 2015 to 2025, and applications of keratin. The study also presented an array of extraction methods comparing their yield, feasibility, and disadvantages. Furthermore, future perspectives and research opportunities for safer methods, hybrid systems for targeted therapy, stimuli-responsive systems, gene delivery systems, bioinks, and personalized medicine were also hypothesized. The review also presented some challenges and limitations, including breaking the extensive disulfide linkages using toxic, non-eco-friendly chemicals; variability in amino acid composition among different keratin sources, resulting in difficulty in standardization and reproducibility; and limited in vivo studies, which have limited the clinical application of the developed systems. Future research should focus on developing greener extraction technologies, standardizing keratin-based formulations, and conducting comprehensive preclinical and clinical evaluations to facilitate its successful integration into pharmaceutical and biomedical practice.

Keywords: *Amino acids, Applications, Drug delivery, Keratin, Sources*

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INTRODUCTION

Conventional dosage forms such as tablets, capsules, suspensions, injections, and topical formulations have been widely used for drug administration due to ease of manufacture, convenience, and cost-effectiveness. However, these dosage forms possess several limitations that can compromise therapeutic efficacy. Oral dosage forms often suffer from poor bioavailability due to enzymatic degradation and extensive first-pass metabolism, resulting in reduced drug concentrations reaching the systemic circulation. Furthermore, many drugs exhibit poor aqueous solubility, low permeability, short biological half-lives, and non-specific

distribution, necessitating frequent administration and increasing the risk of adverse effects. Injectable formulations, although capable of bypassing first-pass metabolism, are associated with pain, poor patient compliance, risk of infection, and the need for trained healthcare personnel. Similarly, topical and transdermal formulations frequently encounter challenges associated with inadequate drug penetration across biological barriers such as the stratum corneum [1]. To overcome these challenges, modern drug delivery systems have focused on developing carriers that protect drugs from degradation, enhance bioavailability, enable controlled and targeted release, and improve patient compliance. Polymers have emerged as key components in these advanced delivery systems due to their ability to form matrices, nanoparticles, hydrogels, films, and scaffolds that regulate drug release kinetics and improve therapeutic outcomes [2]. Previously, synthetic polymers such as poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and polycaprolactone (PCL) were extensively investigated for drug delivery applications. Although these polymers exhibit desirable mechanical properties and controlled degradation characteristics, concerns regarding toxicity of degradation products, limited biocompatibility, environmental sustainability, and high production costs have stimulated interest in natural polymers [3]. Natural polymers have gained considerable attention because they are biodegradable, biocompatible, renewable, and often possess intrinsic biological activity. Examples include chitosan, alginate, collagen, gelatin, silk fibroin, hyaluronic acid, and keratin. These biomaterials mimic components of the extracellular matrix, facilitating cellular interactions and minimizing immunogenic responses. Consequently, they have become increasingly important in designing sophisticated drug delivery platforms for targeted and sustained therapeutic applications [4]. Among natural polymers, keratin has emerged as a potentially attractive biomaterial. Keratin is a structural fibrous protein abundantly found in feathers, wool, hair, horns, hooves, and other keratinous tissues. Unlike many synthetic polymers, keratin contains bioactive amino acid sequences, such as arginine-glycine-aspartic acid (RGD) and leucine-aspartic acid-valine (LDV), which promote cell adhesion, proliferation, and tissue regeneration. Additionally, its high cysteine content allows the formation of disulfide bonds, providing excellent mechanical stability while enabling environmentally responsive degradation and drug release [5]. Keratin has been explored in drug delivery due to its unique combination of physicochemical and biological properties. Keratin exhibits excellent biocompatibility, biodegradability, low immunogenicity, and the ability to encapsulate a wide range of therapeutic agents, including small-molecule drugs, proteins, peptides, and nucleic acids. Furthermore, keratin can be processed into various drug delivery systems such as nanoparticles, hydrogels, films, sponges, scaffolds, electrospun nanofibers, and microneedles. These systems have demonstrated significant potential for controlled drug release, wound healing, tissue engineering, cancer therapy, ocular drug delivery, and regenerative medicine [6,7]. Another important advantage of keratin is its sustainable origin. Large quantities of keratin-rich agricultural and industrial wastes, particularly poultry feathers and animal hair, are generated annually worldwide. The conversion of these wastes into high-value pharmaceutical biomaterials not only reduces environmental pollution but also supports the development of sustainable and circular bioeconomy practices [6]. Despite these advantages, several challenges remain, including variability in keratin source materials, difficulties in large-scale extraction and purification, use of harsh extraction chemicals, batch-to-batch inconsistencies, and limited clinical studies. Nevertheless, advances in green extraction technologies, nanotechnology, and biomaterial engineering continue to expand the potential applications of keratin-based drug delivery systems, positioning keratin as a promising next-generation natural polymer for pharmaceutical and biomedical applications.

Search strategy

The study used a narrative review approach and literature search was conducted in scientific databases, which included Google Scholar, PubMed, SCOPUS, and Web of Science.

Search terms

Keywords used include ‘keratin’ and ‘keratin in drug delivery’, ‘sources of keratin’, ‘methods of extraction’, and ‘applications of keratin.’ This review presented an overview of keratin, sources, processing techniques, formulation strategies, biomedical applications and modifications, challenges and future research prospects or possibilities.

Inclusion criteria

Keratin-based studies that addressed each research theme were presented from 2015 to 2025.

Exclusion criteria

Experimental studies that do not address the research theme.

KERATIN

Keratin is a naturally abundant protein biopolymer classified as a structural fibrous protein. Keratin is a polypeptide consisting of various subunits called amino acids linked by peptide bonds. Each of these subunits is composed of nitrogen, hydrogen, carbon, oxygen, and sulfur atoms. The molecular structure of keratin (polypeptide backbone) consists of amino acids having a high number of cysteine side chains, which are responsible for its folding. A keratinous matter contains functional groups such as amino (-NH_2), carboxylic acid (-COOH), hydroxyl (–OH), and disulfide (-S-S) due to its high cysteine amino acid content [8]. Most of the functional groups are entrapped in the cross-linked or folded network, mainly due to the disulfide (–S–S–) link. Unfolding of the network by chemical treatment, heat exposes the crosslinked or hidden functional groups and creates more reactive sites for interaction with foreign species.

Keratin molecules undergo some interactions or chemical bonding that link the keratin proteins together, such as the disulfide bonding/interaction, salt bonding, and hydrogen bonding. The disulfide bonds are chemical bonds occurring between two sulfur atoms in an amino acid or different amino acids of a protein containing sulfur. This bond links two different parts of the protein containing sulfur, responsible for the formation of loops or coiled configuration in the structures, which become straight under stress but return to their original form when free from stress [10]. The amino acid composition among keratin molecules from various sources differs, most especially cysteine residues [11]. Cysteine residue contains a mercapto (thiol) group (—CH_2SH) and exists in its oxidized form called cystine. Cystine consists of two cysteine molecules covalently crosslinked by a disulfide bond (—S—S—) that results when a hydrogen atom is removed from the mercapto group of each of the cysteines. In keratin molecules, this bond is permanent, difficult to separate, but is damaged by heat and chemical treatments. Heat disruption separates the bonds between the sulfur atoms and allows the formation of new bonds with other sulfur atoms when necessary. The disulfide bonds of cystines also give the keratin significant stability and its low solubility [6]. The peptide chains (chains of amino acids) of keratin are also linked to each other by hydrogen bonds and structure of the peptide chain is highly determined to an extent by disulfide bonds (—S—S—) of cystine.

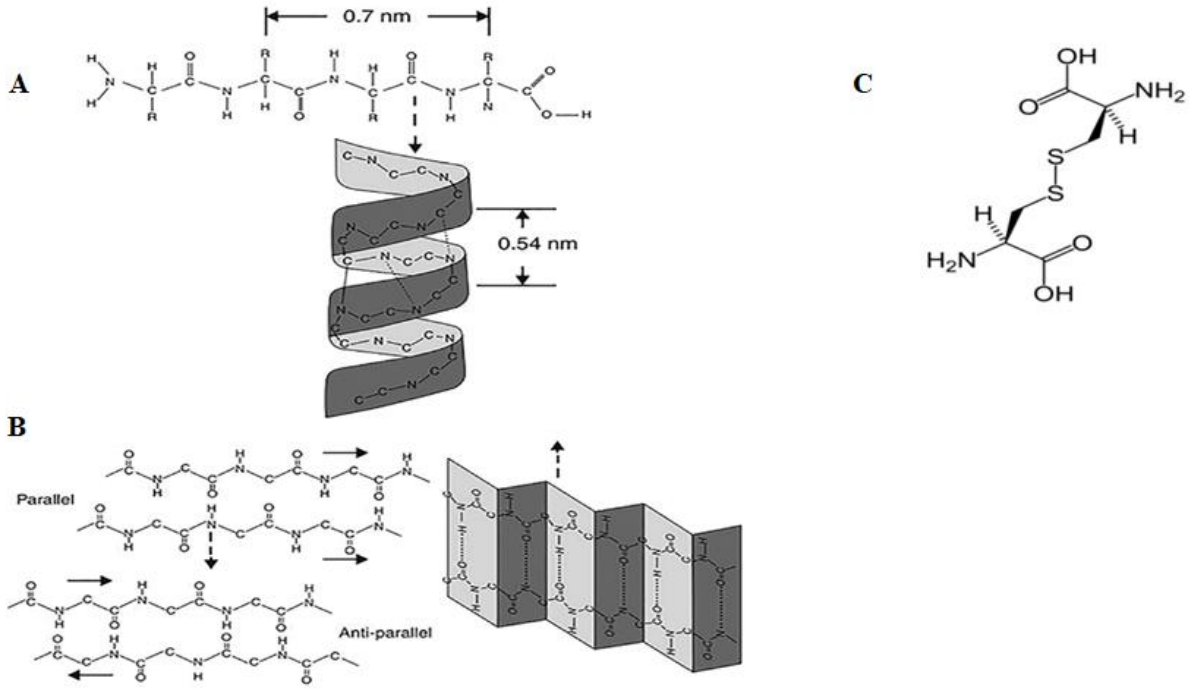

Figure 1: Molecular structure of keratin (A and B), C (Cystine molecule, showing a disulfide (-S-S-) bond joining two cysteine residues) [9]

Commonly, hydrogen bonding occurs between hydrogen and oxygen or hydrogen and nitrogen molecules. These bonds are weak, temporary and are disrupted by water or moisture and heat. The salt bonds or the salt bridges, also confer some stability to the keratin proteins.

Sources of keratin

Keratin protein is distinguished into alpha-keratins (α- keratins) and beta-keratins (β-keratins). Also, the internal structure of every keratin has α-helices and β-sheets. Amino acids of α- keratins form a repeating secondary structure similar to that of an α-helix. Hence, α-keratins are helical in structure, softer (contain less sulfur), and found in all vertebrates, including the hair, skin, and wool of mammals. The β-keratins are harder (high sulfur content) and consist of stacked β pleated sheets, that is, parallel sheets of polypeptide chains found in the epidermis / epidermal stratum corneum of all living reptiles and birds, nails, bird feathers, fish scales, beaks, and claws of reptiles and birds. Keratin has also been obtained from chicken feathers [12,13]. Keratin is wholly insoluble in cold or hot water, not attacked by proteolytic enzymes (i.e., enzymes that break or lyse protein molecules) and hence, not replaced by proteins in the diet. Keratin has a hydrolytic nature (chemical breakdown due to reaction with water). It lacks water retention capacity (that is, it does not retain water) and easily dehydrates at room temperature [8], which may be reduced by the use of polysaccharides like agar, alginate [14] due to their hydrophilicity.

Physicochemical properties of keratin suitable for drug delivery

Keratin possesses several properties making it suitable for fabricating nanoparticles, hydrogels, films, scaffolds, microneedles, and electrospun nanofibers for controlled and targeted drug delivery. These properties include biocompatibility, biodegradability, mucoadhesion, favorable mechanical characteristics, and high drug-binding capacity.

Biocompatibility

Biocompatibility is a fundamental criterion for any biomaterial intended for biomedical applications. Keratin exhibits excellent biocompatibility because it is a naturally occurring protein found in hair, wool, feathers, nails, and skin. Consequently, keratin-based materials generally elicit minimal inflammatory or immunological responses when introduced into biological systems [15]. The amino acids in keratin help to facilitate cellular attachment, proliferation, migration, and differentiation. These interactions are particularly advantageous in tissue regeneration and drug delivery applications where intimate contact between biomaterials and living tissues is required [7].

Biodegradability

Biodegradability is the tendency of a material to enzymatically or biologically degrade into non-toxic products, which are eliminated from the body. The protein backbone of keratin is degraded by proteolytic enzymes. Also, primary degradation products of keratin are amino acids and peptides, which are generally non-toxic and incorporated into normal metabolic pathways [15]. Compared with some synthetic polymers that may produce toxic degradation products, keratin provides a safer and more physiologically compatible alternative.

Mucoadhesion

Mucoadhesion is the ability of a material to adhere to mucosal surfaces, thereby prolonging residence time at the site of administration and enhancing drug absorption. Keratin possesses inherent mucoadhesive properties due to the abundance of functional groups such as amino (-NH_2), carboxyl (-COOH), hydroxyl (-OH), and thiol (-SH) groups capable of forming hydrogen bonds, electrostatic interactions, and disulfide linkages with mucin glycoproteins present in mucus layers. Studies involving keratin nanoparticles have demonstrated prolonged gastric retention and enhanced bioavailability of encapsulated drugs as a result of strong interactions with gastric mucosa [16]. This inherent mucoadhesive property is important for buccal, nasal, ocular, vaginal, and gastrointestinal retention systems, where prolonged contact with mucin is advantageous as it improves therapeutic efficacy and reduces dosing frequency.

Mechanical properties

The mechanical behavior of keratin is a result of the highly organized secondary and tertiary structures, including α-helical and β-sheet conformations, which are stabilized by extensive disulfide bonds. This imparts strength, elasticity, toughness, and flexibility to keratin-based materials [7]. Recent developments in keratin-based electrospun nanofibers have demonstrated favorable mechanical performance for wound healing and sustained drug delivery applications [17].

Drug binding capacity

Due to the abundance of functional groups, keratin is able to encapsulate therapeutic agents. The protein contains amino, carboxyl, hydroxyl, sulfhydryl, and disulfide groups that facilitate multiple drug-polymer interactions, including hydrogen bonding, ionic interactions, hydrophobic interactions, van der Waals forces, and covalent conjugation. This diverse chemistry enables keratin to accommodate a broad range of therapeutic molecules, including hydrophilic drugs, hydrophobic drugs, proteins, peptides, nucleic acids, and growth factors. Furthermore, the presence of cysteine residues enables redox-responsive drug delivery. In reducing environments such as tumor tissues or intracellular compartments rich in glutathione, disulfide bonds within keratin matrices can be cleaved, triggering site-specific drug release. This stimulus-responsive behavior has generated significant interest in keratin-based carriers for cancer-targeted drug delivery and precision medicine [7].

Keratin-based formulation studies between 2015 and 2025

Several keratin-based systems have been developed from 2015 to 2025, which include nanoparticles, electrospun nanofibers, microspheres, and matrix systems (Table 1).

Applications of keratin

Keratin is incorporated into various forms as gels (hydrogels), films, scaffolds, composites, beads and nano/micro-particles. Keratose is a water-soluble keratin and was studied as a bone morphogenetic protein (BMP2) carrier to aid bone regeneration in femoral defects in rats. Results revealed reduction of adipose tissues and improved bone regeneration [35]. Keratin films have also been applied in tissue engineering [36], development of ocular films [37], wound healing [37], membranes [38], carriers [39], biosorbents [40], cosmetics [41,42], bioplastics [43-46], and in agriculture [47,48] (Table 2).

Table 1: Keratin-based formulations studies 2015 – 2025

Keratin-based system	Description	Year	Reference
Keratin/PEO electrospun nanofibers	High-content keratin/poly(ethylene oxide) nanofibers prepared by electrospinning and crosslinking	2015	[18]
Injectable keratin hydrogel	Injectable keratin hydrogel evaluated as filler biomaterial	2016	[19]
Keratin nanoparticles	pH/GSH dual-responsive doxorubicin-loaded keratin nanoparticles	2017	[20]
Keratin-GelMA bilayer scaffold	Bi-layer scaffold of human hair keratin/chitosan nano fiber layer and gelatin methacrylate (GelMA) hydrogel	2017	[21]
Photocrosslinked keratin hydrogel	Visible-light crosslinkable human hair keratin hydrogel	2017	[22]
Keratin nanoparticles	Organic-solvent-free doxorubicin-loaded keratin nanoparticles	2018	[23]
Keratin hydrogel	Tunable keratin hydrogel for rhBMP-2 release and bone induction	2018	[24]
Keratin/PVA/AgNP nanofibers	Electrospun nanofibers from chicken feather keratin, PVA and silver nanoparticles	2019	[25]
Drug-loaded keratin nanofibers	5-Fluorouracil-loaded pH-sensitive keratin/PLLA electrospun nanofibers for local chemotherapy	2020	[26]
Keratin/PBS nanofibrous mats	Regenerated wool keratin-polybutylene succinate mats for drug delivery and cell culture	2021	[27]
Keratin/tragacanth gum nanohydrogels	Nanohydrogel delivery system for medical textiles	2021	[28]
Keratin/hyaluronic acid electrospun fibers	Wound-healing nanofibrous dressing	2021	[29]
Human hair keratin electrospun scaffold	γ-PGA/human hair keratin electrospun nanofibrous scaffold	2022	[30]
Human hair keratin nanoparticles	Keratin nanoparticles synthesized from human hair via sulfuric acid hydrolysis	2024	[31]
Keratin/silk fibroin transdermal patch	Aspirin-loaded electrospun silk fibroin/keratin patch integrated with metallic microneedles	2025	[32]
Keratin/alginate microspheres	Keratin/alginate microspheres as a novel pH-dependent polymer for colon-targeted delivery of dexamethasone	2025	[33]
Keratin/HPMC matrix tablets	Keratin/HPMC matrix tablets for sustained delivery of diclofenac	2025	[34]

Table 2: Applications of keratin

Application	Description	Reference
Tissue engineering	Polystyrene cell culture plates coated with keratin film improved the growth of cells better than uncoated cell culture plates.	[36]
Ocular regeneration	Developed keratin films for ocular surface reconstruction	[36]
Wound healing	Keratin chitosan (KRT/CS) film as a promising therapeutic agent for combined radiation-wound injury.	[37]
Developing membrane	Keratin ceramide was developed for in vitro studies, and the membrane acted as a good model for small drug permeation studies, though unstable in organic solvents.	[38]
Drug carrier for controlled drug delivery	A protein matrix of silk fibroin and keratin from wool to deliver an elastase-inhibiting drug to a wound	[39]
Biosorbent	Adsorbents based on keratin for lead and cadmium removal	[40]
Cosmetics	Low molecular weight (LMW) keratins obtained by liquefying poultry feathers using Fervidobacterium islandicum on MMP-1 and MMP-13 induced by ultraviolet B radiation (UVB)	[41]
	Keratin hydrolysate (KH) infused in ointments	[42]
Bioplastics	Biofilms prepared using 40 % glycerol and chicken feather keratin to test the adsorption of Chromium (VI).	[43]
	Glycerol and hydrolyzed (alkali- based extraction) feather keratin bioplastics, which are prepared by varying the content of glycerol.	[44-45]
	Investigated keratin with polyurethane as a scaffold.	[46]
Agriculture	A multifunctional, eco-friendly fertilizer uses keratin-based superabsorbent as coatings for slow-release urea and remediation of contaminated soil.	[47]
	Keratin hydrolysates obtained from feather decomposition by *Trichophyton ajelloi* on plant germination, growth and biological activity of selected arable soils under model conditions.	[48]

Methods of extraction of keratin

Keratin is difficult to extract because of its high levels of cross-linked disulfide bonds. Therefore, the first required step is to disrupt this intra-molecular crosslink to remove the keratin embedded in the cuticle and cortex layer without destroying the covalent bond of the amino acid chain. Reduction of the disulfide bond of cysteine increases solubility of the feathers and aids keratin extraction. Several methods have been employed for keratin extraction, including chemical methods (reduction, hydrolysis, oxidation, use of ionic liquid), other methods such as microbial and enzymatic methods, use of microwave irradiation, and steam explosion [6].

Reduction method

The disulfide bonds in cystine are broken down using reducing agents to obtain a good yield of keratin from various animal sources [49]. Reduction method includes the use of various reducing agents such as thiol containing chemical (thioglycolic acid, thioglycolate salt, mercaptoethanol (Yamauchi method, Shandai method), sulfitolysis (using sodium sulfide (Na_2S). There have been reports on the use of different reducing agents under different processing conditions, such as denaturing agents and different pH levels [50]. The Yamauchi method involves the extraction of the keratin from wool (Corriedale) using a mixture of urea, mercaptoethanol, surfactant (sodium

dodecyl sulfate, SDS), and water at 40-60 °C. This resulted in a keratin yield of 45–50 %, and the use of the surfactant (SDS) was effective in promoting extraction and improving stability of the protein in aqueous solution [51]. A modified method of Yamauchi's method, known as Shindai method, has also been developed. This involves the use of thiourea and urea with 2-mercaptoethanol (MEC) as reducing agents. Investigation on the Shindai method showed a yield of > 75 % from keratin sources like chicken feathers and wool [52]. Despite this high yield, the protein obtained only remained inside the solution in a reduced form. The use of MEC has been the standard in disulfide bond reduction during keratin extraction due to its high yield and the maintained keratin structure obtained. However, it is a hazardous chemical, with an offensive odour, expensive, not eco-friendly, and may remain as residual solvent, which is a disadvantage when further processing is required.

Sulfitolysis

This involves breaking down the sulfide bonds to a S-sulfonated (R–S–SO3 −) and cysteine thiol (R–S−) residue [6]. Major sulfite compounds used for Sulfitolysis include sodium sulfite, bisulfite, and disulfite. Kamarudin *et al* [50] investigated extraction parameters of keratin from 0.5 g chicken feather using various reducing agents and reported that sodium sulfide (Na_2S) gave the highest yield, 84.5 % of keratin under optimized conditions (80.9 °C, 9.5 h with 0.05 M sodium sulfide). Gupta *et al* [14] reported 53 % yield of keratin protein from 50 g of chicken feather from 0.05 M sodium sulfide at 30 °C and pH of 10-13 for 6 h. Poole *et al* [53] reported 55 % yield from 50 g of feathers at 30 °C. Although this method is eco-friendly compared to the reduction method using MEC, pure sulfitolysis sometimes gives less soluble protein than harsh thiol-based reduction methods.

Hydrolysis (alkaline) method

This method involves the use of alkaline solutions for hydrolysis and acids for neutralization. The primary chain of keratin is damaged and structure is disrupted in the hydrolysis method. The high concentrations of alkali isolate the hydrogen from sulfur nucleus and carboxylic groups and enable solubilization, despite damage to the peptide chains [54]. Breakdown of these bonds leads to exceptionally bad odour perceived during the treatment. Some drawback with this method includes damage to the protein backbone, use of a high quantity of alkaline and acid to counteract the alkali and precipitate the protein. Some studies have been reported using this method.

A report on extraction from 20 g chicken feathers using 2.5 % NaOH solution (pH 13, 70 °C for 75 min) yielded 34.8 % keratin [55]. Izabela *et al* [56] compared the yield from different concentrations of sodium hydroxide using 10 g defatted feathers stirred at 50 °C for 2 h and reported 94 % keratin yield. Alashwal *et al* [57] reported that keratin was efficiently extracted from 50 g of feathers at 50 °C, stirred for 5 h; however, no report on yield was documented. Meko *et al* [12] used alkaline hydrolysis to isolate keratin from chicken feather wastes. This is quite easy, and reagents used are not very expensive. However, the very alkaline conditions are capable of destroying or converting certain amino acids. Also, this process requires large amounts of acid (for example, HCl) to neutralize the solution and precipitate the keratin.

Oxidation method

Earland and Knight [58] and Buchanan [59] were early researchers to report oxidation methods for the extraction of keratin. They used peracetic acid and performic acid, respectively, to obtain a solubilized homogeneous solution. Often, it has been reported that the entire wool keratin is not dissolved using this method, as it is not a homogeneous material. Hence, residues of insolubilized keratins are often found, which are postulated to be β-keratin. The α-keratin, which has a crystalline form, is believed to be solubilized, whereas the β part forms a jelly-like material. Proteins extracted via oxidation (keratosis) are modified synthetically and the disulfide bonds of the cysteine are changed over to sulfonic acids. In this way, these proteins may have diverse physicochemical properties compared to the keratins acquired through other methods. Brown *et al* [60] evaluated effectiveness of the different methods, including peracetic acid or percarbonate to oxidize disulfides and reported a viable method for all reagents used in terms of cost effectiveness. The extracted proteins (keratose) offer excellent aqueous solubility and film-forming capabilities, making them highly suited for drug delivery systems and biodegradable protein films. The strong oxidizing capacity of the agents may destroy critical amino acids, compromising the overall nutritional and structural profile of the protein.

Ionic liquid

Ionic liquids (ILs) are salts consisting of ions (cations and anions) existing as liquids below

100 °C. They have some unique properties, such as low vapour pressure, non-flammability, high thermal stability, and non-volatility, hence they are recognized as green liquids. A major drawback of using this method is that keratin extraction is done under an inert atmosphere (N_2) because of the hygroscopic nature of the ionic liquids, and requires expensive specialized equipment [61]. Ji *et al* [61] used ILs {Amim}Cl, {Bmim}Cl and {Bmim}Br to extract keratin and added 10 % Na_2SO_3 (to aid breakdown of the disulfide bond) in an extraction time of 1 h at 90 °C from feathers and reported a 75.1 % keratin yield. Idris *et al* [62] reported 60 % keratin yield from dissolution of turkey feathers in ILs (under nitrogen at 130 °C for 10 h) without any other solvent or chemical added. Although the yields obtained are high, and the use of ionic liquid is a greener method, the high production costs and complex methods have hindered usage and scalability.

Future perspectives and research opportunities

Need for safer methods

Future research should therefore pioneer greener, safer, and more cost-effective extraction strategies that significantly preserve the native integrity of keratin while improving yield and industrial scalability. There is also the need to modify existing extraction methods that may improve solubility, mechanical strength, and processability without compromising biocompatibility.

Development of hybrid systems

Furthermore, hybrid systems that combine keratin with other natural or synthetic polymers, either by chemical crosslinking or other physical methods, which may improve performance and widen biomedical applications, should be pursued. Other research opportunities also exist in the design of keratin-based platforms for targeted and sustained drug delivery, regenerative medicine, and advanced wound dressings. Comparative and systematic studies evaluating keratin from different waste biomass sources would be needed to identify the most suitable raw materials for specific applications.

Need for in vivo studies

Also, more studies are required to investigate structure–property relationships, optimize formulation parameters, and assess the performance of keratin-based systems under physiological conditions. These efforts will support the transition of keratin from an underutilized waste-derived protein to a versatile biomaterial with significant pharmaceutical and biomedical relevance.

Keratin nanocarriers for targeted therapy

The abundance of cysteine residues, disulfide bonds, and cell-binding active sites in keratin provides unique opportunities for the development of targeted nanocarriers capable of selectively delivering therapeutic agents to diseased tissues. Surface functionalization of keratin nanoparticles with targeting ligands, such as antibodies, as in the case of antibody-drug conjugates, peptides, folic acid, aptamers, and transferrin, to facilitate receptor-mediated uptake by cancer cells should be pursued.

Such modifications may improve drug accumulation at tumor sites while minimizing systemic toxicity. Furthermore, keratin nanoparticles may be engineered to exploit the enhanced permeability and retention (EPR) effect for passive tumor targeting. The integration of imaging probes and therapeutic agents into keratin nanocarriers may also enable theranostic applications for simultaneous diagnosis and treatment of diseases [20,23,63].

Stimuli-responsive keratin systems

Development of smart keratin-based delivery systems that respond to physiological and external stimuli remains a promising research direction. Due to the presence of disulfide bonds, keratin may be engineered to undergo structural changes in response to redox conditions commonly observed in tumor microenvironments. Future studies should investigate pH-responsive, temperature-responsive, enzyme-responsive, light-responsive, magnetic-responsive, and reactive oxygen species (ROS)-responsive keratin systems for controlled and site-specific drug release. The incorporation of multiple stimuli-responsive mechanisms within a single keratin carrier may further enhance therapeutic precision and efficacy while reducing adverse effects [20,26].

Keratin-based gene delivery systems

Gene therapy has emerged as a promising strategy for the treatment of genetic disorders, cancers, and infectious diseases. The challenge of efficient and safe delivery of nucleic acids still exists. Future research should explore keratin-based systems for the delivery of plasmid DNA, messenger RNA (mRNA), small interfering RNA (siRNA), microRNA (miRNA), and CRISPR-Cas

gene-editing components. The presence of reactive amino acid residues in keratin allows chemical modification and conjugation with cationic polymers to enhance nucleic acid loading and intracellular delivery. Development of keratin-based non-viral vectors may provide safer alternatives to viral gene delivery systems by reducing immunogenicity and cytotoxicity while maintaining high transfection efficiency [35,64].

Keratin/exosome hybrid systems

Exosomes have attracted considerable interest as natural nanocarriers because of their excellent biocompatibility, low immunogenicity, and intrinsic cell-signaling functions. Future studies should investigate the combination of keratin biomaterials with exosomes to develop hybrid delivery platforms capable of improving exosome stability, retention, and sustained release. Keratin hydrogels, nanoparticles, and scaffolds could serve as reservoirs for exosome delivery in wound healing, tissue regeneration, neurodegenerative disorders, and cancer therapy. Such hybrid systems may offer synergistic benefits by combining the structural properties of keratin with the biological activity of exosomes [15,65].

Keratin bioinks for 3D bioprinting

Three-dimensional (3D) bioprinting has revolutionized regenerative medicine by enabling the fabrication of patient-specific tissues and organ constructs. Keratin possesses several desirable properties for bioink development, including biocompatibility, biodegradability, and the presence of cell-adhesion motifs. Future research should focus on optimizing keratin-based bioinks through blending with biomaterials such as gelatin methacrylate (GelMA), alginate, collagen, and hyaluronic acid to improve printability, mechanical strength, and cellular interactions. Keratin bioinks may find applications in the fabrication of skin, bone, cartilage, nerve, and vascular tissue constructs, as well as in drug screening and disease modeling platforms [15,66].

AI-assisted formulation optimization

Artificial intelligence (AI), machine learning (ML), and computational modeling are increasingly transforming pharmaceutical research and development. Future investigations should focus on applying AI-driven approaches to optimize keratin extraction processes, predict drug-loading capacities, model release kinetics, and identify optimal formulation parameters.

Machine learning algorithms may facilitate the rational design of keratin nanoparticles, hydrogels, and scaffolds by reducing experimental workload and accelerating formulation development. The integration of AI with high-throughput experimentation could significantly improve reproducibility and reduce the time and cost associated with developing keratin-based drug delivery systems [67,68].

Personalized medicine

The increasing emphasis on personalized medicine presents significant opportunities for the advancement of keratin-based delivery systems. Future research should explore patient-specific keratin formulations designed according to genetic profiles, disease characteristics, and therapeutic requirements. The use of autologous keratin sources, such as human hair-derived keratin, may reduce immunogenic responses and improve biocompatibility. Additionally, the integration of keratin biomaterials with 3D printing technologies, wearable biosensors, and precision diagnostic tools could facilitate the development of individualized drug delivery platforms capable of optimizing therapeutic outcomes for specific patients [64,69].

Challenges and limitations

Despite the considerable potential of keratin as a biomaterial in drug delivery and related biomedical applications, there are several challenges that continue to limit its full application. Keratin is difficult to extract from its natural sources because of the extensive disulfide crosslinks, making it highly stable and poorly soluble. Also, many conventional extraction procedures require harsh and toxic chemicals, elevated temperatures, prolonged processing times, specialized equipment, specialized handling and processing, which may increase cost, result in environmental hazards, and alter the native physicochemical characteristics of the protein.

Furthermore, keratin obtained from different sources, such as poultry feathers, wool, hair, and animal skin, showed widespread variability. As a result, differences in amino acid composition, cysteine content, and molecular architecture may influence yield, purity, biodegradability, mechanical strength, and functionality. This variability will thus make standardization and reproducibility difficult and complicated, especially if intended for sensitive biomedical applications such as controlled drug delivery, wound healing, and tissue engineering. Also, the

absence of robust *in vivo* studies to elucidate the long-term safety, stability, and therapeutic effectiveness of the experimental dosage form has hindered further development into clinical practice.

CONCLUSION

Keratin sourced from various biomaterials, including poultry feathers, wool, and animal skins, has been used to develop functional biomaterials and delivery systems. Obtaining keratin from these sources required several methods, with yield as the optimized outcome. Furthermore, it has undergone modifications in the past, such as oxidation with hydrogen peroxide. This improvement has led to better physicochemical profile and improved delivery performance. Despite the numerous advantages, scalability, use of harsh chemicals, variability in keratin sources, and absence of extensive *in vivo* studies have limited its widespread application. Future studies should therefore seek more green, safer, cost-effective methods or modify existing methods that improve solubility, mechanical strength, and processability without compromising biocompatibility. Functionalized carriers, stimuli-responsive systems, gene delivery systems, bioinks, and personalized delivery systems should be pursued. Also, *in vivo* studies on the performance of various keratin-based systems under physiological conditions would espouse various biomedical possibilities and translate these systems into clinical practice.

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Conflicts of interest

The authors declare no conflict of interest.

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