Chapter 2
Keratin Production and Its Applications: Current and Future Perspective

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Abstract Keratin is a global class of biological material, which represents a group of cysteine-rich filament-forming proteins. They serve as a shielding layer for the epidermal appendages like nails, claws, beak, hair, wool, horns, and feathers. These proteins are further subdivided into two different class based on their secondary structure: α-keratin and β-keratin. Keratin is insoluble in hot or cold water; this unique property helps to prevent their digestion by proteolytic enzymes. Additionally, their complex hierarchical-like filament-matrix structure at nanoscale and the polypeptide chains create a robust wall for protection against heat stress,

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pathogen invasions (particularly through skin), mechanical damage, etc. In this review, we are trying to attempt a linear focus in the direction of structure, function, extraction of keratin, and its industrial applications.

Keywords Keratin · Keratin structure · Keratin production · Keratin application

1 Introduction

Natural elements like carbon, nitrogen, oxygen, sulfate, and phosphorous and also some proteins produced by bacteria including green fluorescent protein, etc., have superabundance impact on living system, and most of them are beneficially using in life science and molecular engineering. Virtually, all the biological materials are robustly consisting of biopolymers and some minerals. Such combination represents excellent properties and functionalities in many biomolecules (Wang et al. 2016a). In the early 1800s, there was no specific name of protein and was considered in the category of "albuminoids". Around 1849, one novel word "keratin" was appeared in the literatures that represent different properties and attract the scientist's attention for understanding the novel behavior of this hygroscopic protein. Keratin belongs to a very diverse family of fibrous protein. Keratinous material like horns, wools, nails, feathers, and hooves are the global class of biological co-products, which represent a group of cysteine-rich filament-forming proteins. Moreover, keratins are the protein that forms a shielding layer for the epidermal appendages and thereby imparting an important role in protection. The spacious arrangement of disulfide overpass significantly influences the keratin properties, in particular broad chemical and mechanical resistance. Keratin is insoluble in hot or cold water; this unique property helps to prevent their digestion with proteolytic enzymes such as pepsin, papain or trypsin (Bohacz 2017; Staron et al. 2011; Tesfaye et al. 2017).

Epithelial cells of cytoplasm are the richest compartment for keratinous structural protein, in which they were assembled into a network of 10–12 nm wide intermediate filament (Kim and Coulombe 2007). In human genome, almost 54 conserved genes encode keratin protein and these genes are further subdivided into type A and type B subgroupings of intermediate filament (IF)-encoding genes (Table 1) (Schweizer et al. 2006). There are 28 classes of type A and 26 classes of type B genes and each type of gene encode for a single polypeptide chain. Type A proteins are smaller and more acidic while type B protein is larger and more alkali than type A family (Schweizer et al. 2006). Type A and type B proteins interact together and form a heterodimer that promotes polymerization of keratin (Steinert et al. 1976; Fuchs and Cleveland 1998; Kim and Coulombe 2007). The arrangement of keratin is mediated by type A as well as type B genes and thus maintains the integrity of epithelial cell lines, but, on the other hand, their improper arrangement and misfolding may lead to severe epithelial disease such as epidermolysis bullosa

Table 1 Subgrouping of IF-encoding genes

Protein family	Size (kDa)	Pi
Type A	40–64	~4.7–6.1
Type B	52–70	~5.4–8.4

simplex (Coulombe and Lee 2012). In this review article, we briefly discuss the structure, function, source, and industrial application of keratin, and finally few important priorities as conclusion.

2 Structure and Classification of Keratin

Keratin is a global class of biological material, which represents a group of cysteine-rich filament-forming proteins. Keratin is the second most essential and abundant biopolymer that confronts in animals (Sharma and Gupta 2016; Sharma et al. 2016, 2017a, b, c, 2018). They serve as a shielding layer for the epidermal appendages like nails, claws, beak, hair, wool, horns, and feathers (Shavandi et al. 2017a, b). Their complex hierarchical structure like filament-matrix composition at nanolevel and polypeptide chains creates a robust wall for protection against heat stress, pathogen invasions (particularly through skin), mechanical damage, etc. (Kadir et al. 2017).

Keratins and keratinous materials are subdivided into two different classes of secondary structures of protein: alpha (α)-keratin and beta (β)-keratin (Shavandi et al. 2017b). On the basis of X-ray diffraction pattern, these proteins can also be classified as α-pattern of keratin, β-pattern of keratin, amorphous, and feather pattern of keratin (Fraser et al. 1972; Astbury and Woods 1934; Fraser and Parry 2011). The amorphous pattern elucidates the amorphous matrix component in α-keratinous tissue (Staron et al. 2011), while the feather pattern shows similarity to β-pattern (Fraser et al. 1972).

2.1 *α- and β-Keratins*

Keratin is made up of long polymerized chain of amino acids, and molecular weight of keratin in feather is about 10,500 Da (Staron et al. 2011). These α-helix and β-plated sheet structures arise due to the continuous folding of the backbone of the polypeptide chain due to hydrogen bonding between carboxyl and amino groups of the peptide chain. The structural configuration of α- and β-keratins is represented in Fig. 1 along with 3D structure of keratin protein.

In α-helical structure, polypeptide chain forms a hydrogen bond with the maximum possibilities of their interaction between carbonyl group of one amino acid and amino group of another amino acid. The diameter of α-helix structure is 7–10 nm, and their molecular mass is in the range of 40–68 kDa (Wang et al. 2016b, Alibardil et al.

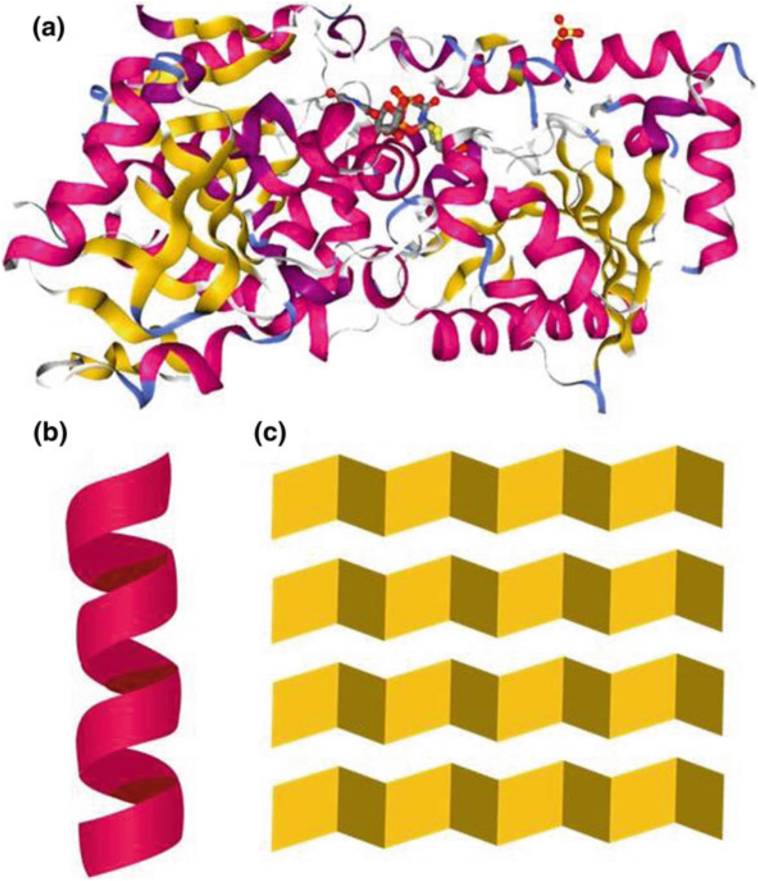

Fig. 1 **a** Schematic representation of 3D structure of keratin protein, **b** α-helix is formed by twisting of polypeptide chains into screw manner, and **c** β-sheet structure is the result of maximum extension and stretching of polypeptide chains

2006). α-Keratin is a most abundantly found in mammals. Such type of structure is organized as coiled coil and thereby participating in compact structural arrangement to elongate polypeptide chain (Crick 1952, 1953). On the other hand, β-structure carries intermolecular hydrogen bonding between carbonyl and amino group. The diameter of β-structure is about 3–4 nm and molecular mass is about 10–22 kDa (Table 2). These types of structure are most abundantly found in reptilian tissues, such as feathers, claws, and beaks of birds, etc. (Chen et al. 2012).

Table 2 Structure-based comparison and distribution of α- and β-keratins

Characterization	α-Keratin	β-Keratin
Bonding	Intramolecular hydrogen bonding	Intermolecular hydrogen bonding
Diameter (nm)	7–10	3–4
Structural features	Intermediate filament matrix	Amorphous matrix
Molecular mass (kDa)	40–68	10–22
Distribution	Wool, horns, hairs, nails, and hooves	Avian beaks, feathers, claws, reptilian epidermis, and claws
Stiffness	High	Lower than α-keratin

3 Sources of Keratin

Sources of keratin include wools, nails, hairs, hooves, feathers, reptilian scales, and avian (Fig. 2). Reptilian scales, feathers, and avian display almost similar keratin genes (Gregg et al. 1984), and it has been also proved that these feathers and scales are β-sheet based on transmission electron microscope (Filshie et al. 1964) and X-ray diffraction patterns (Astbury and Marwick 1932; Fraser and Parry 2008).

3.1 Feather, Beaks, Wool, and Hair

Since very early days, humans are very fascinated with understanding the concept of how birds can fly, and how birds (like duck) can protect their wings during swimming or rainy condition. You have been already noticed that the bird's wing does not get sloppy, easily during rain or rainy season. So, this is mainly considered keratin (β-form) protein may involve for providing mechanical support to the feather, and thereby prevents feather to get sloppy. To further understand this concept, Filshie and Gogers (1962) analyze feather under transmission electron micrographs, and their study reveals the filament-matrix structure with the β-keratin filaments. This structure was about 3 nm in diameter and embedded in an amorphous matrix.

The keratinous material is also present in rhamphotheca (outer surface layer) of bird beaks, and it allows the beaks to participate in a variety of functions, like feeding, social interactions, fighting, and grooming (Luester 2006). Usually, bird beaks fall into two categories: (1) long thin and (2) short/thick except in toucan beak, as it is both thick and long (Wang et al. 2016b). Wool and hair is the remarkable example of the hard-keratinous material. Wool is the excellent animal fiber, containing 82% keratinous protein. It is widely used in textile application and is scientifically important because of its mechanical and structural behavior (Feughelman 1997).

Hair is another widely used and studied fiber. Study on hair and wool revels that they both have common features except wool has large diameter. In many cases, hair plays an important role in terms of protection against dust and pathogens (hairs in nostril).

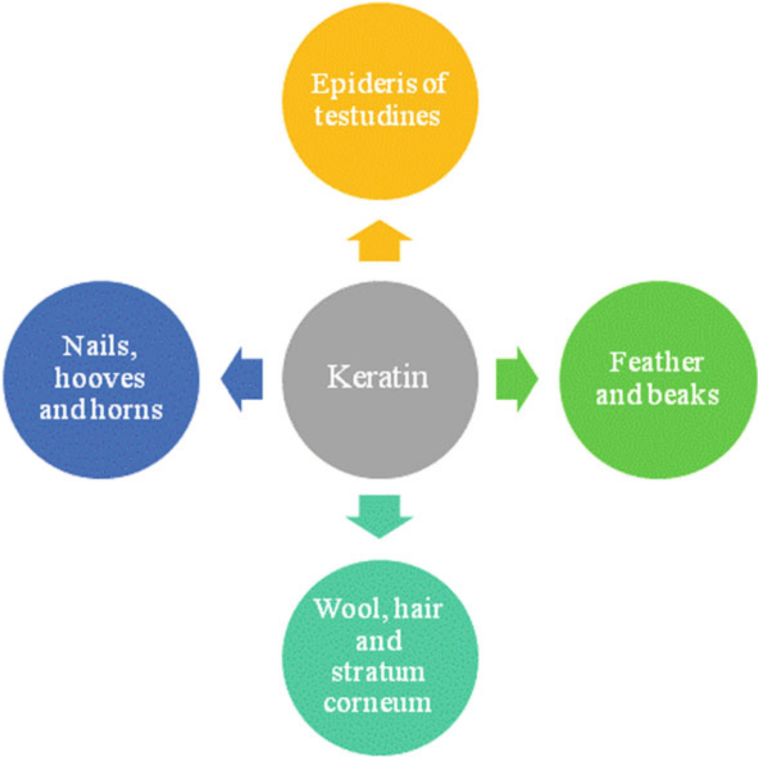

Fig. 2 Different sources of keratin

3.2 Stratum Corneum, Horns, and Hooves

Light and skin interaction regulates the optical visibility of the skin to human eye. Skin can absorb and reflect light in a diverse manner (Lee et al. 2018). Skin is also responsible for regulating the body's temperature, and it is actively participated in defense mechanism by acting as a barrier for pathogen(s). Mammalian skin is covered by outermost layer of stratum corneum, and the thickness of this layer is about 20–40 μm (Tomlinson et al. 2004). This layer act as defense layer from external attack (predators) and serve as diffusion barrier (Meyers et al. 2008).

Stratum corneum is composed of keratinocytes; these cells are embedded in an intracellular matrix that is highly rich in lipid content. Their cytoplasmic content is arranged in web-like pattern and robustly integrates at cell-to-cell junctions. Such interaction(s) in a diversely integrated manner maximize the mechanical support (Coulombe and Wong 2004).

Bovid animals like cattle, waterbuck, sheep, buffalo, and gazelle carry keratinous material in the form of horn. Horns act as a weapon, sometime(s) as shield to protect from predator and combat with other animals for their defense (Trim et al. 2011).

It may also involve for regulating body temperature (Geist 1966). These are highly tough, and can show resistance against opposite force, but cannot grow, once it gets broken (Tombolato et al. 2010). Hooves are the toughest keratinous materials and are still being an attractive topic for the research. Hoof wall is composed of flattened, keratinocytes. Hooves have a complex structure, and these complexities allow the hoof wall to absorb enough energy as the crack grows (Cook et al. 1964).

3.3 Epidermis of Testudines and Nails

The group "Testudines" usually represents the turtles, tortoises, and terrapins. Recent studies on Testudines indicate turtles are rich in both α- and β-keratins (Dalla Valle et al. 2013). The β-keratin/α-keratin ratio is higher in the carapace in hard-shelled turtle. This ratio provides an important factor for further study in the background of keratin.

Nails are the important source of α-keratin. In primates and few mammals, it covers the ends of the fingers and toes (as their ends have soft skin, so indirectly these proteins participate in protection). In cats, these protein forms curved claws and show α-type pattern during the analysis under X-ray diffraction pattern (Bear and Rugo 1951). Fingernails are one of the important features in primates (Hamrick 1998), as they can use their nails during fighting, scratching, and opening of some object.

4 Various Methods Used for the Keratin Production and Degradation

Poultry, meat, and leather processing industries generated every year large amount of keratin-containing wastes. Globally, every year, poultry processing industries generate around 8.5 million feather waste (Fellahi et al. 2014). Currently, these keratins-containing waster products are buried, dumped, and used as land filing, which generates problem in storage, ash disposal, and emission control (Agrahari and Wadhwa 2010). Here, we are trying to focus on some important methods for keratin production and degradation (Fig. 3).

4.1 Hydrolysis of α- and β-Keratins by Bacterial Cultures

The static extension of poultry industry facilitates a huge amount of wastes. Recycling of such waste(s) does not affect the environmental pollutant problems, but it also improves the rate of keratin production for various purposes. Poultry meat

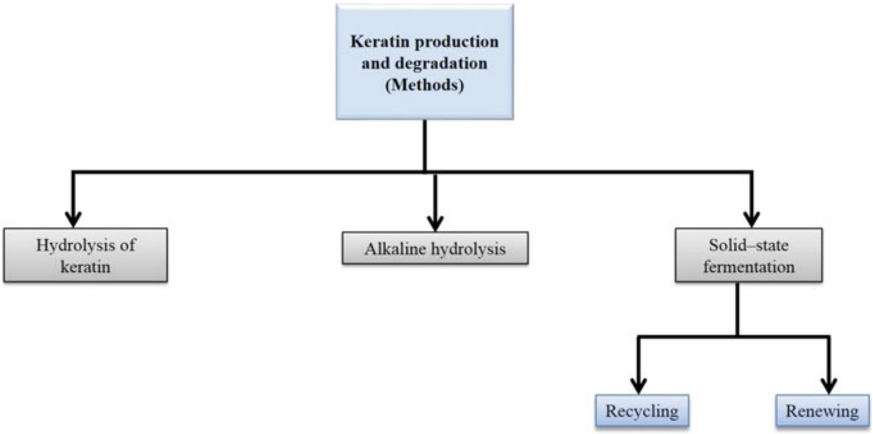

Fig. 3 Methods of keratin production

industries provide gigantic waste such as bones, feathers, and viscera. Bioconversion of such wastes into the useful material using a specific enzyme(s) is a fascinating paradigm. Presently, enzymes are widely used at broad spectrum for the conversion and production of poultry waste into feeding and fertilizers.

Keratin proteins separated from feather by several chemical modifications. Poultry (including birds) feathers contain around 90% keratin along with some important amino acids like cysteine, threonine, and arginine (Sinkiewicz et al. 2017; Tiwary and Gupta 2012).

Initially, protease (keratinases, EC 3.4.99.11)-producing microorganisms were isolated, screened and most potent protease-producing microorganisms were identified. The microbial enzyme (protease) attacks insoluble keratinous protein substrates and thereby releasing free amino (–NH_2) group containing molecules (Abdel-Naby et al. 2017; Bagewadi et al. 2018). In order to check the hydrolysis property of keratin components, different kinds of substrates like chicken feather, sheep wool, pea pods and more were used as substrate. Generally, after hydrolyzing, these substrates were further proceed by following chopping, washing, and then overnight incubation at 60 °C. Finally, freely released of amino acids were analyzed at 0–3 days of interval (Fellahi et al. 2014). The brief summary of keratin production is summarized in Fig. 4.

4.2 *Production of Keratin Using Alkaline Hydrolysis*

Keratin production and their extraction can also be done by alkaline hydrolysis. Extraction and production, these two processes mainly depend on two different complementary factors (1) chemicals, as it is important for extracting spe-

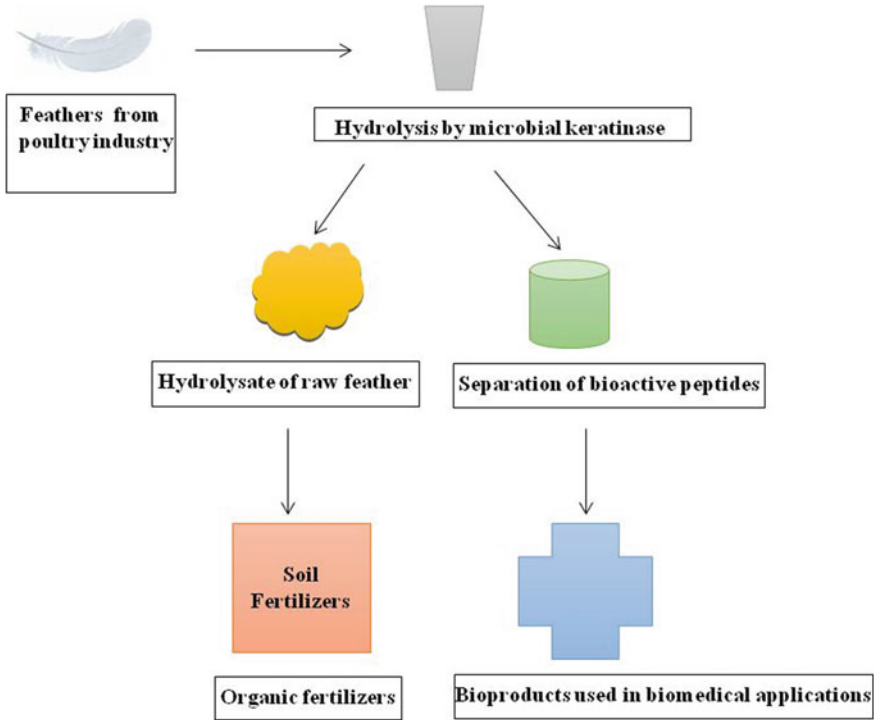

Fig. 4 Microbial keratinase activities for the conversion of wastes from poultry industry to useful by-products. Following hydrolysis, the hydrolysates can be used as organic fertilizers, and these hydrolysates can also be used in biomedical applications

cific cellular proteins from the cell, tissue or organ, and (2) optimal condition(s), as it is important, because, it provides all the ideal support for protein stability. For example, keratin from bird's feather can be obtained by alkaline hydrolysis method. During the process chemicals like ammonium sulfide or sodium sulfide can reduce disulfide group to thiol group. And also, by using β-mercaptoethanol, free –SH group can be partially modified. The process was carried out for 90 min at 45–80 °C. The obtained keratin molecular weight was approximately between 1 kDa and 11 kDa (U.S Patent 2007). Recently, Sinkiewicz et al. (2017) demonstrated the influence of thermochemical treatments using different reducing agents (2-mercaptoethanol, dithiothreitol, sodium m-bisulphite, and sodium bisulphite, as well as sodium hydroxide) on the production of keratin (in chicken feathers extract). 2-Mercaptoethanol and sodium bisulphite treatment yields about 84% and 82% of keratin. Additionally, sodium hydroxide (2.5%) was further improved the production of keratin up to 94% (Sinkiewicz et al. 2017).

4.3 Solid-State Fermentation (SSF) for Keratin Degradation

Keratinases are the enzymes having proteolytic activity for the keratin degradation (Bagewadi et al. 2018). Consumption and utilization of poultry animals as the food product tremendously increase the consequence of biowaste, and it is very difficult to degrade such wastes within the short period of time. Keratin and their keratinous component, carries numerous amino acids, and their decomposition in the form of feather does not only cause environmental problem but it also leads to loss of several important amino acids that can be used in making nutrient-rich food products.

Solid-state fermentation (SSF) is a booming industrial process in biotechnology and microbiology field; it is mainly used for recycling or renewing biological waste(s) at large scale. In this process, microorganism grows in aqueous-free environment or sometimes at very low water content (Saratale et al. 2014). Submerged fermentation is the analogue of solid-state fermentation in which all the natural conditions are optimized and they mimic the natural environment (Bagewadi et al. 2018; Soccol et al. 2017). Chitturi and Lakshmi (2016) demonstrate an attractive method for keratinase production using *Bacillus strains*. The beneficial trait of this research was indicated as an improved method for keratinase production, and the yield was increased from 283–367 KU/mL to 415–442 KU/mL (Chitturi and Lakshmi 2016). Not only bacterial cultures, but the keratinase enzyme can also produce from fungal culture(s) under optimal conditions (Bagewadi et al. 2018), as it has a great influence on the feather degradation. SSF is eco-friendly process, significantly contributing to minimize the bio-pollutants and to maximize the area for food industries (Bagewadi et al. 2018).

5 Industrial and Clinical Applications of Keratins

It is very difficult to degrade keratins and their disposal may lead to serious harmful impact on the environment. Therefore, research should be proceeding by focusing on keratin waste utilization (Bagewadi et al. 2018; Bohacz 2017; Karthikeyan et al. 2007). India has broad livestock populations, which display annually: 82 million goatskins, 30 million sheepskins, and 28 million buffalo hides (Karthikeyan et al. 2007). Around 8–10% of chicken weight is due to their feather and approximately millions of tons of feather are generated annually (Karthikeyan et al. 2007). Besides this, a large quantity of horns, hairs, hooves, and feathers are wasted every year (Onifade et al. 1998). From the past few years, these wastes are utilizing at industrial level to extract some important and insoluble (keratin) proteins. To get rid of this serious threat, there are various applications that can utilize these biowastes to convert them into beneficial form. Polyvinyl alcohol fibers that contain keratin were found to be an extensive industrial application, for example; they can be used as absorbents for toxic/hazardous substances like heavy metals ions as well as formaldehyde gas (Rouse and Van Dyke 2010).

5.1 Alkali and Hydrothermal Treatment

Hydrothermal treatment depends on high steam pressure of 10–15 psi with or without high temperature (80–140 °C) in the presence of acidic solutions (hydrochloric acid, sulfuric acid and more) (Eggum 1970) or alkali solution (sodium hydroxide, potassium hydroxide, sodium carbonate and more) (Gousterova et al. 2003; Papadopoulos et al. 1985). Combining acid or alkali treatment at the boiling temperature for about 2-3 h could open disulfide bridges of keratin and forms water-soluble polypeptides and oligopeptides or sometimes few amino acids. The crucial point of this process is the degradation of amino acids and polypeptide chains at high temperature that affects the nutritional improvement values.

5.2 Use of Keratin in Leather Industries

Keratin is a biopolymer having multifunctional properties, and these properties make (turn on the pathways of) keratinous material utilization at industrial level. Systematic optimization of the keratinous component form biological waste products, participate in recovery of natural resources and aids in maintaining pollution free environment (Niculescu et al. 2016).

Wool is the keratinous material having well-defined structure and mechanical properties (Wang et al. 2016b). Wool fiber contains approximately 82% of keratinous protein and high percentage of cysteine, around 17% along with small number of polysaccharides and lipid wax (Lewis and Rippon 2013). All these properties made keratin useful in leather industries (2007).

5.3 Keratin in Drug Delivery System

Drug delivery is a dynamic process which involves the process of administration of drugs, their absorption, and interaction with the target site. For many drug applications, drugs are designed in such a way that it should be able to provide maximum desired therapeutic effect or drug efficacy with less toxicity (Nelson et al. 2002; Parveen and Sahoo 2008). Drug delivery should be maintained in a controlled manner; if the condition for drug delivery is not maintained at high level, then it may cause serious complications, and even it may lead to the death of the person. Moreover, a diverse family of polymers have been identified in drug delivery purposes. Drug delivery already has been achieved by using synthetic and natural polymers. Synthetic polymers including polyphosphazenes, polyorthoesters, polyanhydrides, polyesters, and polyphosphoesters have found in broad application (Nair and Laurencin 2006), while natural polymers including collagen, cellulose, gelatin, and alginates are broadly used because of their biocompatibility and biodegradability (Malafaya et al. 2007; Mano et al. 2007).

Over the last few years, keratin is widely used for the drug delivery system (DDS) in a controlled manner because of their stability, less reactivity, structural, and mechanical properties. Being natural polymer, keratins have advantage as it is rich in reactive chemical groups like amide, carboxyl, hydroxyl, as well as sulfhydryl, and hence, these properties enhance their activity to interact with biologically active molecules. One simplest way of incorporating drugs into keratin biomaterials is to dissolve or mix before processing into the keratin solution. Such protocols were designed for the synthesis of drug loaded keratin films (Fujii et al. 2004; Vasconcelos et al. 2010). For example, Li and co-workers developed a nano-based PEG-induced keratin method for drug delivery to treat cancer (Li et al. 2012).

5.4 Keratin in Surgery and Repairing

Keratins have complex bio-protectant and strong structural properties. They show similar properties to collagen like insolubility, high tensile strength, etc., and these properties illustrate the importance of keratin in surgery.

Partial and peripheral burns are the consequence of patient management with respect to multiple dressing. It is important to protect the skin from infection, wound, trauma, and external injuries to minimize the possibilities of major (supreme) damages in skin and thereby, promoting rapid epithelial cells proliferation (Loan et al. 2016). Skin is the outermost layer of the body that protects every living organism from serious threats and it also regulates homeostasis during unfavorable conditions. Loan and co-group reported that “keragel and keramatrix” (keratin-based products) can be used during damaging of dermis and epidermis layers (Loan et al. 2016).

Skin injury and their repairing possibilities can be enhanced by stimulating migration activity of keratinocytes at injured, damaged, and wounded site(s). These proliferation and migration rate of keratinocytes significantly promote basal membrane’s protein expression including types IV and VII collagens (Tang et al. 2012) and show improvement in clinical trials such as skin surgery, leg ulcers (Hammond et al. 2010), and in epidermolysis bullosa (Than et al. 2013).

6 Conclusion and Important Aspects

Keratin depicts toughest and significant biological material; act as protective integument in mammals, primates, and in Testudines. Keratin has compact structural and robust mechanical properties which attracts life science researchers for the proper understanding of physical, chemical, and biological properties of keratin. For example, keratinous materials provide the toughest source for protection (nails over the skin, horn, and hooves in horse), feeding and interaction (outermost layer of beaks).

Research on keratin is directed toward the advancement of numerous biomaterials having keratin for practice in application of biomedical field. For example, in recent days, hair damage (caused by UV radiation from sunlight, pollution, and nutrient deficient food supplements) can be repaired by synthetic treatment of keratin. Although such treatment is temporary, still it is widely used in metropolitan area to minimize hair loss. Additionally, keratinous materials have diverse hierarchal structures and functions that can be useful for development or architecture of new structure for the human benefit. In spite of the fact that remarkable research has been conducted on keratin, still some area of research is unclear and insufficient. Here, we are now trying to put some important factors that may illustrate some beneficial points in keratin research:

- Although a significant amount of details is available for keratin, α- and β-keratinous material are not well understood, including their biosynthesis, molecular assembly, gene sequence, mechanical, and structural nature. This indicates and opens a new door in research for diverse investigation of keratinous material.
- Keratin has high mechanical and compact biological properties, this knowledge we can apply on synthesizing and assembly of new products with low molecular weight and high mechanical strength.
- To predict the novel structure and their function, it is essential to understand the morphological and structural configuration relationship.
- More studies required to understand the importance of keratin-based nanomaterials that may be useful for drug delivery and providing therapeutic response.

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