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Pharmaceutical & Cosmetical Application of Keratin Protein Obtaining from Biowaste- A Review

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ABSTRACT

Keratin is a fibrous structural protein and major component of hair, horns, claws, hooves, feather, wool, hoof and outer layer of skin. These keratinous materials are formed by cells filled with keratin and are considered 'dead tissue'. Keratin acts both as an external protective protein & internal structural protein in the cortex. It is insoluble in water and organic solvents. Keratin can be derived from the human and animal sources by the advancement in extraction, purification and characterization process. It consists of highly repetitive amino acid sequences which result in formation of various homogeneous secondary structures. Keratin has been processed in oxidized and reduced forms in term of keratose and kerateine which shows strong mucoadhesive properties in drug delivery systems. It can also be processed as keratin hydrolysate by using acid, alkali and enzyme. Especially for hair care products, skin treatment and harsh products such as detergents, shampoos, conditioners etc. As it does not contain any harmful effect, it can be used to produce variety of cosmetics and pharmaceutical products. In addition, extracted keratins are capable of forming self-assembled structures that regulate cellular recognition and behavior. These qualities of keratin led to the development of biomaterials with applications in wound healing, drug delivery, target release action, tissue engineering, trauma and medical devices. This review discusses the natural sources of keratin and their derivatives and application of keratin biomaterials in pharmaceutics and cosmetics.

Keywords: Keratin, keratin hydrolysate, Phytokeratin, Biomaterials, Drug delivery, keratin film, Nanoparticles, cosmetics.

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INTRODUCTION

Several efforts have been made for the development of green materials. Yet there is much left to replace chemically synthesized materials with biodegradable and environmental friendly biomaterial in pharmaceutical and other industries. A ubiquitous biological materials, keratin is cysteine rich protein widespread in biological tissues, being a major functional component. The solubility and structural integrity of keratin including biocompatibility, biodegradability, bioactivity, non-toxicity, low cost & easy to process makes it an ideal polymer.^[1]

Keratin can be classified in to Alpha, Beta and Gamma keratin. Alpha keratin is found in hair fibers, Beta in hair cuticle, which is protective in function, and Gamma keratin is present in hair follicle. It contains higher sulphur content.^[23] Its disulfide and covalent bonds are mainly responsible for its chemical and mechanical resistance.^[2] Animal-derived keratins seem compatible with human biological system if it is carefully extracted from the source. It is used as platform technology to make biomaterials for biomedical applications.^[3] The ability of extracted keratin to self-assemble in to three dimensional porous structures has led to its development as scaffolds for biomedical applications.

BIOLOGICAL SOURCES OF KERATIN

Keratin is found in a human skin, hair, nails. It also found in reptiles, birds, amphibians and other mammals^[4] sometime including the hooves of animals.



It also found in the spider web and silk of silkworm.^[5] Chicken feathers consist of approximately 90% of total protein and it is the ideal material for obtaining keratin from waste biomass of poultry industries.

Phytokeratin is a composite product made by blending free amino acids from plants in the same proportions as that of found in popular human hair amino acid products. Some phytokeratins are the Hydrolyzed Soy Protein, Hydrolyzed Corn Protein and Hydrolyzed Wheat Protein responsible for the Moisturizing, Film-forming and Moisture binding effects.^[58]

CHEMICAL COMPOSITION

Keratin is cysteine rich protein widespread in biological tissues being a major functional component. Cysteine is present in human hair 14 to 15% , 8% in horse hair and 3% in horse's hoof, etc.^[59] Keratin contains histidine , lysine, and arginine which are present in the molecular ratios of approximately 1:4:12. Keratin composed of Sulphur, Tyrosine, tryptophane, Phenylalanine, Glycine which are present in very small quantity i.e. approximately 2 to 3% and 15% nitrogen.^[60]

The feather proteins have an amino acid composition in the high proportion of glycine and serine. The amino acid composition of feather keratin showed only minor changes when the proteins were subjected to fractionation, so the feather keratins differ markedly from the mammalian keratins, which can be fractionated into the major families with characteristic compositions and molecular size. The feather keratins were shown many years ago to be homogeneous and to have a low molecular weight.^{[61][62]}

Amino acid analysis of chick feather keratin in mol%

[SCMK- S (thioglycollate content) carboxyl methyl keratin]

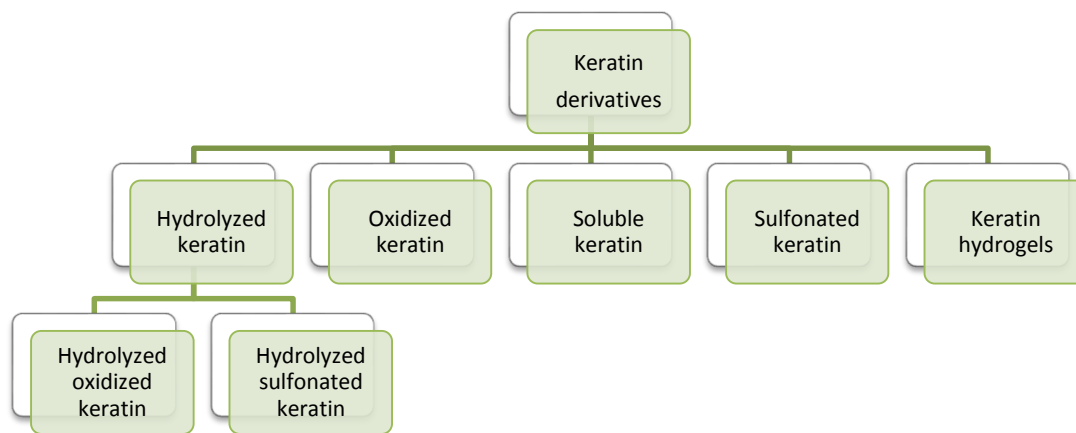
Residue	Whole rachis	SCMK extract
Alanine	8.7	8.6
Arginine	3.8	3.6
Aspartic acid	5.6	3.4
Half cystine	7.8	8.2
Glutamic acid	6.9	6.8
Glycine	13.7	13.9
Histidine	0.2	0
Isoleucine	3.2	3.2
Leucine	8.3	7.8
Lysine	0.6	0.1
Methionine	0.1	0
Phenylalanine	3.1	3.3
Proline	9.8	10.5
Serine	14.1	15
Threonine	4.1	3.9
Tryptophan	0.7	0.7
Tyrosine	1.4	1.2
Valine	7.8	8

METHODS OF PREPARATION AND ITS DERIVATIVES

- The chicken feathers are first dissolved by using suitable reducing agents and then precipitated protein is collected by using ammonium sulphate solution^[6] which can be used to made films, hydrogels, micro particle, nanoparticles for purpose of food, cosmetology, medical, agriculture and other products. ^[4]

- *Phytokeratin* is a composite product made by blending free amino acids from plants in the same proportions as that of found in popular human hair amino acid products. Some phytokeratins are the Hydrolyzed Soy Protein, Hydrolyzed Corn Protein & Hydrolyzed Wheat Protein. They are used for the Moisturizing, Film-forming and Moisture binding effects.^[58]
- Keratin was obtained by oxidative extraction yielding keratose powder and further resuspended to form hydrogels and the drugs ciprofloxacin ^[52] and halofuginone ^[53] incorporated in this step through the electrostatics interactions.
- Hydrolyzed keratin can be obtained by addition of hydroxyl group in to the structure of keratin protein. Keratin is hydrolyzed by acid, alkali or by using the enzymes to convert it into hydrolyzed keratin. ^[7]
- Hydrogels are formed from keratins obtained by oxidative preparation are called as keratose.^[64]

Keratin can be processed in various forms, some of which mentioned below. ^[24]



TOXICOLOGICAL STUDIES ON KERATIN PROTEIN

According to a recent study, hydrolyzed keratin sourced from hoof meal, & sheep wool was found to be non-irritant, non-mutagenic in an oral study (Rat).^{[27][28]} No dermal irritation and ocular irritation of keratin(5%) was predicted in rabbit study.^{[28]-[31]} Repeat dose toxicity and carcinogenic effect of keratin had yet not found in any relevant publication.

PHARMACEUTICAL APPLICATIONS

Nano particles

The incorporation of drugs into the nanoparticles is best option for increasing the efficiency of the particular drug. According to recent studies keratin based nanoparticles are very effective anticancer drug-carriers possessing a degree of tumor targeting ability. ^{[10][11]} This tumor targeting

ability of nanoparticles is attributed to their pH sensitivity.^[11] Recent research studying of efficient strategy to control and regulate the mucoadhesion and drug release of keratin based nano drug delivery system and the revaluation of keratins in different pH conditions are helpful for the design and development of mucoadhesive drug delivery system.^[32]

Gold nanoparticles, coated with keratin exhibit **antibacterial activity** against *S. aureus* (Bovine Mastitis Bacteria) with biocompatibility.^[12] It also possess **antioxidant activity**.^{[14][15]} Recently, an article reported the development of keratin-g-polyethylene glycol nanoparticles loaded with doxorubicin (DOX) and indicated that the loading efficiency increases with the increase of the keratin content on the keratin-g-PEG nanoparticles due to the formation of hydrogen bonds between keratin and drug. Higher release rates are obtained at intracellular level with efficient internalization showing the promising applications of keratin-g-PEG as drug carriers for cancer therapy^{[56][11]}.

Silver nanoparticles coated with keratin act as an **anti-cancer agent** are shown to have improved stability in aqueous environment.^[13] Now a days, there is much progress in treatment of collagen by using keratin-based materials.

Keratin film

These biomaterials are widely used in pharmaceuticals. Generally biomaterials are integrated into devices or implants and must be compatible with the transplanted body. Some keratin films which prepared by using solvent casting technology are used for production of films having much high quality requirement.^[1] Keratin films prepared from numerous hair samples since it is highly sensitive and reproducible. Keratin film is suitable for the efficient screenings of many chemical and natural substances. Keratin obtained from poultry feathers are modified with glycerol, which acts as a plasticizer. The films are “tough” and the mechanical properties show similarities to the properties of commercially available thermoplastics. The keratin films were produced in a few minutes without reducing or oxidizing agents.^[40] Keratin films are able to withstand chemical and physical stimulations such as UV, perm, bleach and thermal treatments.

According to recent study on keratin film was found to be used for **ocular surface reconstruction** as human amniotic membrane very effectively.^[17] it was proposed as an alternative carrier and showed to be suitable for corneal epithelial cell expansion. These film based materials can be successfully implanted in to a corneal stromal pocket in vivo. They causes a mild inflammatory response which can be controlled by using low dose of topical steroids.^[63]

Micro needles

It improve the patient compliance, transdermal delivery of drug is more convenient and suitable, because it avoids first pass effect and gastric irritation. Keratin micro needles have been successfully used to deliver drugs and other components such as serum, albumin, bovine albumin and calcein suggesting their safety and potential in delivery of drug.^[34]

Keratin hydrogels

Recently discovered that keratin hydrogels have homeostatic properties and it have ability to absorb fluid and may be effective hemostat.^[19] The keratin gels applied on injury site, by instigating thrombus formation and by forming a seal or mesh like structure on the wound site that acted as a scaffold to allow for granuloose tissue formation.^[36]The ability for keratin protein-based biomaterials to be translated into the human is elucidating the mechanisms by regulating **hemostasis** and **nerve regeneration**.^{[37][38]}

These hydrogels are effective polymeric system for *tissue engineering* as well as regenerative medicine application because it supports the sustained release of therapeutic agents. Some reports are describes the use of hydrogels for sustained release of antibiotics; which is useful for *bone regeneration*^[18] and preventing traumatic injury, acute infections.^[64]

Keratin based drug delivery system and their sustained & controlled release actions

Keratin based biomaterials are capable of providing sustained and controlled release of antibiotics as effectively formulated for inhibition of bacterial growth both in vitro and in vivo. These types of formulations are compatible with mineralized component for a combined treatment modality to inhibit bacterial infection from trauma and battle field injuries and promote bone generation. ^[33]

The drugs *ciprofloxacin* ^[52] and *halofuginone* ^[53] incorporated in this step through the electrostatics interactions. Keratin-ciprofloxacin and keratin-halofuginone hydrogels formulation support the sustained release action of the drugs over 3 weeks and 7 days respectively, with pharmacological activity. In a recent study, *diclofenac* drug was added to keratin solution to prepare drug- keratin films. These were further crosslinked with *transglutaminase* and the results indicated that *diclofenac* release is closely related to the solubility of keratin films. ^[54]

The presence of free cysteine residues in keratin sponges allows the immobilization of bioactive agents. Lysozyme was immobilized in a keratin sponge via thioether bonds and disulfide bond.^[55]

Other pharmaceutical products

Keratin used as biomaterials for the preparation of keratin sponges, Scaffolds, Keratin fiber and in Tissue engineering.^[16] It can be processed in to various forms, for e.g. micro particles for improving the technology of Drug release action.^{[22][35]} It recently discovered for *peripheral nerve repair* and *wound healing*.^{[20][21]}

COSMETICAL APPLICATION

Proteins are the basic building blocks for today's skin and hair care products. Proteins are isolated from a variety of sources and possess properties that are essential for the care and protection. According to VCRP (Voluntary Cosmetics Registration Programme) data which analyzed in year 2016, verified that *Hydrolyzed keratin* was the most reported ingredient in safety assessment of the cosmetic product. [23] There are various approaches to convert the keratin protein in to hydrolyzed keratin. [4]

Hydrolyzed keratin acts as a humectant which reduces loss of water from the dermal layer of skin. [26] It is particularly useful for treating hair that has been damaged due to permanent Waving & Bleaching because it has protective colloid effect which reducing the chapping and irritancy caused by detergents and other harsh products. Hydrolyzed keratin is also very effective moisturizer for the skin. [9]

These type of cosmetics products improved elasticity and hydration properties. [25] It has reported maximum concentration of use i.e. up to 5 % used in dressing, hair tonics and other growing pharmaceutical aid. [23]

- Appearance: Clear amber liquid
- Volatility: 1gm/Hr/105°C
- pH: 5.5 to 7.0
- Microbial count when packed: 100 O.P.G. max no pathogens. [8]

Formulations for hair

Keratin was able to improve both mechanical and thermal properties of normal hair. It was compatible with water environment supporting its application as a cosmetic product. [41] However, the study of its cytotoxicity and genotoxicity indicated that decreased cell viability and skin irritation. The peptide linkage (which contains mainly cysteine amino acid) was found to be non-cytotoxic, and it does not inhibit cell growth nor induce DNA damage or DNA crosslinking in human foreskin. [42]

Keratin-based protein has biological evaluation and strengthening properties on relaxed hair. [43] Shampoo containing keratin will strengthen human hair, rebuild damaged hair and keep it from further breakage. [44] Recently discovered straightening cream is used to straighten the kinky, curly, or even wavy hair. There is a number of hair straightening compositions of creams, shampoo and conditioners available today, but a correct composition and methods are needed to produce better and safe formulation. [45]

Treating wool keratin with urea is generally known to swell the wool fiber to allow permeation of treatment solution beyond the surface cuticle in hair.^[51]

Keratin Complex Smoothing Therapy

The recent innovative technology in Smoothing Therapy treatments binds keratin to the hair. This process helps prevent humidity from penetrating the hair, thus locking out frizz. In addition, Keratin Complex Color Therapy incorporates this signature keratin technology into the hair-coloring process, which helps to make the hair stronger and smoother as it undergoes a color transformation

In skin care product

In the long-term study, the beneficial effect of application of *wool keratin* samples on healthy skin has been demonstrated. Hydrolysed keratin protein derived from wool may be applied alone or combined with wool internal lipids structured improving in both cases the elasticity, hydration and moisture sorption–desorption profile.^[48] This new combination of derivatives from wool fiber can be suitable for designing new cosmetic or pharmaceutical products for skin care because internal wool lipids are rich in cholesterol, free fatty acids, cholesterol sulphate and ceramides.^{[46][47][49]}

It has an effective moisturizing ability to penetrate down through the top six layers of the epidermis, enhancing the moisture content of the skin, Gives skin a soft, healthy appearance for the skin.^[58] As with collagen proteins, it is substantive. Since Hydrolyzed keratin is a primary constituent of skin, it makes good sense to use a protein of this type in skin preparations. Keratin hydrolysate acts as a humectant (it binds water from lower layers of the epidermis to the stratum corneum) as well as an occlusive (it reduces trans-epidermal water loss). Adding keratin hydrolysates to the ointment base did not cause phase separation even after 6 months storage.^[50]

Keratin based nail cosmetic products

There is limited source of human nail plate for studying drug permeation, for the treatment of various nail diseases. Keratin can be extracted by using reductive conditions and its films prepared by the method of solvent evaporation. The produced films were suitable for permeation experiments regarding to its water resistant property and mechanical stability.^[57]

A highly effective daily keratin protein treatment that helps repair damaged nails with the power of keratin protein. Is the **RESCUERXX™ DAILY KERATIN TREATMENT** product, Keratin Protein is a main component of the natural nail. Solubilized keratin proteins bond to the natural nail to help strengthen the nail plate.

In others cosmetics

Some of derivatives of keratin may be used in products that can come into contact with the eye or mucous membranes. For example, hydrolyzed keratin is used in mascara at up to 0.2% and in detergents and bath soaps at up to 0.028% and also was reported to be used in hair sprays at a maximum concentration of 0.059%. Additionally, some of these derivatives were reported to be used in hair sprays and could possibly be inhaled.

CONCLUSION

It is concluded that keratin which is obtained from biomass like human hair, nails, animals, horns, claws, hooves, feather, wool, hoof and outer layer of skin and plant such as maize, wheat and rice has vast applications in pharmaceutical industry. As natural keratin is less effective but its processed forms are very effectively used in various fields like preparation of biomaterials, nano particle, different drug delivery systems which having sustained and controlled released actions, multiple pharmaceutical preparations of hydrogels, films and various types of cosmetic products. These animal keratin and phytokeratin can be used very safely on human being. This is one of the major step for the reducing the waste of biomass including plants and animals.

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