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Valorization of keratin waste biomass and its potential applications

Chilakamarry Chaitanya Reddy [a], Irshad Ahamad Khilji [b], Arun Gupta [a,*], Prakash Bhuyar [c], Syed Mahmood [a], Khater Ahmed Saeed AL-Japairai [a], Gek Kee Chua [a]

[a] Faculty of Chemical and Process Engineering Technology, Universiti Malaysia Pahang, Gambang, Pahang, 26300, Malaysia
[b] Faculty of Manufacturing and Machactronics Engineering Technology, Universiti Malaysia Pahang, Pahang Darul Makmur, Pekan, 26600, Malaysia
[c] Faculty of Industrial Sciences and Technology, Universiti Malaysia Pahang, 26300, Malaysia

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ABSTRACT

Keratin is a major structural protein with high sulphur content. It is predominantly found in chicken feathers, wool, hair, hoof, and nails. Over the years, the accumulation of keratin waste has become an uncontrollable entity throughout the world. Environmental aspects may reduce the load of waste generation by waste process engineering. Such studies focus on the safe and effective conversion of keratin-based slow degradable wastes by green methods. Different methods of waste-conversion, like chemical and thermal, have been discussed. Various keratin degradation methods have been investigated like hydrolysis under pressure by using steam, enzymatic and chemical hydrolysis. The significance of keratin with potential applications and aid in the advancement of several environmentally sound bioproducts are described, including various keratin utilisation methods with its applications. More advantageous are enzymatic and bioconversion methods which assure milder conditions and preserve nutritional properties of the produced biomass. Keratinous wastes can be used as feedstock; however, appropriate processing is required to valorise the waste. In the present scenario, the accumulation of waste is causing water pollution, environmental damage and threatening human lives is discussed. At the end of the article, various critical applications, including waste process engineering, are summarised. This review concludes with a study on the conversion of keratinous waste into consumable products to minimise pollution.

1. Introduction

Over recent decades, high wastewater amounts have been produced by agricultural activities, industrialisation and global urbanization [1]. The repeated wastewater disposal in the absence of enough and appropriate treatment may lead to severe pollution problems. Eutrophication phenomenon is recognised as a pollution problem concerning the discharge of effluents into the water bodies. The peripheral effluents of wastewater contain nutrients, commonly phosphorus and nitrogen. Under this phenomenon, the influx of these nutrients from wastewater promotes the growth of aquatic plants, thus resulting in depletion of dissolved oxygen [2]. Eutrophication leads to depleted oxygen levels in water and increases levels of toxic compounds like ammonia which causes deterioration of freshwater ecosystems [3]. Thus, effective treatment methods are needed to reduce nitrogen and phosphorus content in the wastewater.

The increase in the activities related to habitable human development like rapid urbanisation and overutilisation of natural resources including mining has led to the release of massive volumes of different types of wastes into water bodies [4]. Electroplating, fertilisers, metals, pesticides, paper and mining industries produce toxic metals like arsenic (As) [2], cadmium (Cd) [5], copper (Cu), chromium (Cr), iron (Fe), lead (Pb) [6], silver (Ag) and zinc (Zn). These metals are non-biodegradable, possess high density in water even at low concentrations, thus gathering in living organisms and soil [7]. Biological consumption of these metals is risky for healthy humans [8]. Agriculture-based industries produce a large amount of waste that increases environmental pollution, which adversely impacts human and animal health.

A vast amount of untreated agricultural waste creates different problems with the climate by increasing greenhouse gas effect [9]. Agricultural waste comprises of animal waste (chicken feather, manure and animal carcasses) and food waste (vegetables, fruits, sugarcane,

Abbreviation: CF, Chicken feather; W, Watt; kDa, Kilodalton; U ml^{-1}, Units per milliliter; *w/v*, weight per volume; *w/w*, Weight per weight; MPa, Megapascal pressure; H, Hour.

* Corresponding author.
E-mail address: arun@ump.edu.my (A. Gupta).

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maise, *etc*). Chicken feathers are part of agricultural waste, and about 5 million tons is produced as a waste stream per year during meat processing [10]. Only minor amounts are consumed as animal feed in low grade, and bulk amounts are disposed of, thus causing a significant environmental threat [11].

Industrial, commercial and domestic wastes are removed by proper waste management processes that deal with appropriate waste treatment to reduce environmental pollution and maximise product recovery. However, it is still a challenge for several industries to dispose of their waste in an eco-friendly manner. Innovative and sustainable solutions are needed to reduce pollution efficiently. Adverse environmental impacts can be avoided to a great extent by using bio-based and recycled materials or renewable resources instead of fossil fuels.

Several proteins like collagen, albumin, gelatin, fibroin and keratin have been investigated in the development of naturally-derived biomaterials. However, keratin is of paramount importance in bringing a revolution to the biomaterial world due to its mechanical durability, intrinsic biocompatibility and biodegradability. Keratin-based biomaterials serve as favourable biosorbents for removal of metals from wastewater [12].

Chicken feathers can be used as one of the major sources for extracting keratin as they contain 90 % of crude keratin protein, 70 % of amino acids, high-value elements, vitamins, and growth factors [13]. Keratin has high mechanical strength and consists of 20 amino acids which are linked together by forming peptide bonds that contain a covalent disulphide bond, hydrogen bond, hydrophobic and ionic bonds [14]. The various methods used to extract keratin are reduction [15], oxidation [16], alkali extraction, microwave irradiation, steam-explosion [17], sulfitolysis and ionic liquid dissolution [18].

Keratin has various applications in biotechnological, waste management, cosmetic and medical sectors [19]. There is an excellent need for economic and environment-friendly strategies to convert waste feathers into keratin. This review summarises recent progress in biodegradation of chicken feathers, its environmental impacts, and keratin production. Furthermore, keratin types and its characteristic features, methods of extraction and various applications are described. The focus is on its application as a biosorbent for water purification by removing toxic heavy metals.

2. Impact of keratin waste on environmental pollution and human health

Rapid industrialisation and urbanisation is a vital part of modern culture and has resulted in increased waste generation. Keratin waste is collected in vast amounts from marketable poultry production plants, leather factories, wool industry, textiles industry and slaughterhouses (Fig. 1). These residues arising from industrial waste can pose a significant threat to environmental conditions and human lives (water, air and soil) [20].

Fig. 1. Keratin waste generation by various industry.

Keratin waste is generated from slaughterhouses in enormous quantities in the form of feathers, beaks, bones and hard tissues. Slaughterhouse wastewater has been characterised as highly polluted wastewater and is known to have a negative impact on the environmental biodiversity. The wastewater has high levels of biological oxygen demand (BOD) and chemical oxygen demand (COD) due to decay of organic matters like flesh, blood, fat and excreta. High amounts of nitrogen and phosphorous are present in wastewater which are released into water bodies [21]. The release of biodegradable organic compounds reduces the level of dissolved oxygen in surface water [22]. The phenomenon of eutrophication comes into play where nutrients (nitrogen and phosphorous) from organic compounds released into water bodies stimulate the growth of aquatic plants, thus leading to depletion of oxygen stores [23]. Nitrate leaching and pathogen transfer to groundwater affect the quality of drinking water. Ramirez et al. estimated the carbon-dioxide production from poultry slaughtering to 18 million tonnes [24]. Poultry production has a negative environmental impact leading to land, water and air pollution with greenhouse gas emissions like (nitrous oxide and carbon-dioxide). Nitrous oxide is released due to the high concentrate feed requirement due to the use of nitrogen fertiliser. The other greenhouse gas, carbon dioxide is produced during fertiliser manufacturing [25].

Poultry processing plants produce significant amounts of feathers as a waste by-product. Approximately 8.5 billion tons of poultry feathers are produced yearly worldwide [26]. Accumulation of chicken feathers can lead to environmental pollution and have a severe impact on people's lives in surrounding areas [27].

Keratin wastes are produced in significant amounts from the poultry industry (slaughterhouses) in the form of chicken feathers, beaks, mixtures of bones, organs and hard tissues. Keratin waste is processed gradually and is deemed to be toxic waste in compliance with EU directives [28]. Contaminated wastewater produced by these factories creates problems with soil acidification, eutrophication, and decreases biodiversity [29]. The modern methods of handling keratin waste are expensive and quite challenging. Decomposition methods, like incineration, are used [30], which also impacts on the environment adversely.

Leather industries generate toxic pollutants which are hazardous to the environment. A large quantity of keratin waste produced by the leather industry is in solid and liquid waste forms and is mostly of animal origin [31]. The leather industries are responsible for the inefficient discharge of large amounts of keratin waste (fur, horns and hoofs), thus polluting the environment and causing serious health issues [32].

The barber and nail artist shops are equally responsible for causing pollution. Human hair is considered to be a toxic pollutant and is a significant source of urban waste in the country [4]. It accumulates in vast amounts as solid waste and chokes the drainage systems. In rural areas, hair wastes are generally thrown away and decompose slowly over the years. Open dumps of hair generate hair-dust; if inhaled in large quantities, it may lead to several respiratory problems [33].

3. Keratin protein

Keratin belongs to a group of insoluble proteins known as intermediate filaments (IFs), cytoskeleton element with a size of 8–10 nm. IFs are not soluble in traditional protein solvents and are not digested with trypsin or pepsin. The term keratin appeared in the literature around 1850 to describe the material that formed hard tissues like hooves and horns. The Greek word "kera" means horn. Keratin is a fibrous protein, rigid in nature, and is the third most abundant polymer in the ecosystem after chitin and cellulose. The classification of keratin protein is represented in the Fig. 2. Based on the X-ray diffraction pattern keratin exists in two different structural forms, namely Alpha (α)-keratins (α-helix

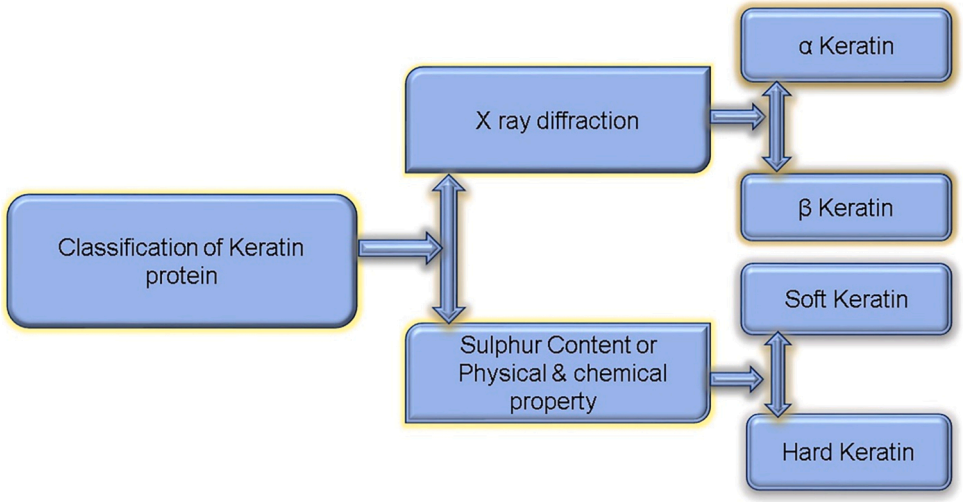

Fig. 2. Classification of keratin protein.

structures) and Beta (β)-keratins (β-sheet structures) [34]. Alpha keratin is present in the epithelium of all vertebrates [35] and animal body parts and tissues like horn, hooves, hair, nails and wool [36]. The α -helix in alpha keratin is resistant to microbial degradation and thus poses an environmental concern. Alpha keratins have great strength, durability, resilience, and insolubility [26]. They are made of hydrophobic amino acids, *i.e.* methionine, phenylalanine, valine, isoleucine and alanine. In specific, α-keratins are made of two sub-filaments based on molecular weights, Type I and Type II. Type I is the acid keratin with 40, and 50 kDa and Type II is the neutral or basic keratin with 55–65 kDa [37].

Beta-keratin is a functional protein found in nails, claws, shells, and beaks of birds with a molecular weight of 10–14 kDa. Beta-keratin has an intense cysteine concentration which readily constructs disulfide bonds that impart rigidity and resistance to oxidation [38]. Approximately 80–90 percent of β-keratin is found in mature feather.

The sulfur content is a deciding factor of the hardness and softness of keratins. Keratins with <3% of sulphur are soft keratins mainly found in skin, particularly stratum corneum. Hard keratins are those with >3% of sulphur and are found in hair, wool, feather, nails and horns [39].

4. Techniques for the valorisation of keratin waste

For many years now, a variety of methods have been established to extract keratin utilising acids and alkalis, reduction, oxidation, sulfitolysis, dissolution in ionic liquid, enzymatic and chemical-free hydrolysis (represented in Fig. 3). Among the various extraction methods, dissolution by ionic liquids, enzymatic and chemical-free hydrolysis (steam-explosion, microwave treatment and use of superheated water) have gained importance for being environmental-friendly.

4.1. Enzymatic and microbial methods

Enzymatic and microbial treatment plays an essential role in hydrolysing the peptides from keratin-rich materials that can have biotechnological or nutritional applications. Microbial pathways consist of enzymatic activities, and nearly all synthetic enzymes are involved in hydrolysis reactions [45]. The hydrolysis process of keratin enzymes involves minimal aspects of treatment, utilises less energy, and is environmental-friendly. Keratinases are proteases that are microbes

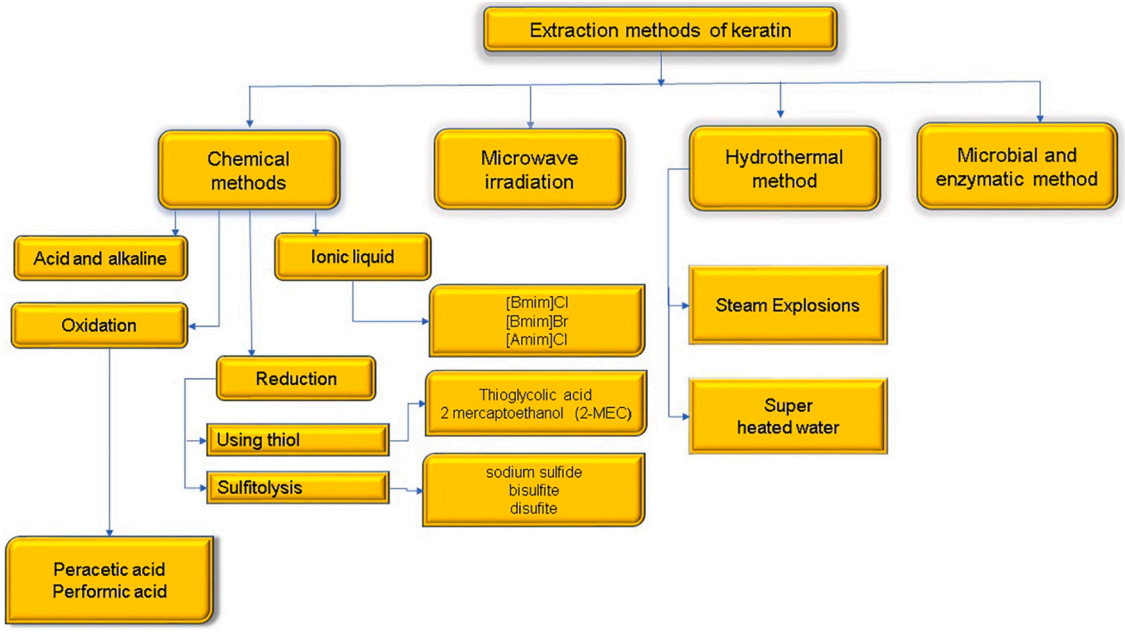

Fig. 3. Extraction methods of keratin protein.

with some hydrolysing microorganisms [42]. The microbial-enzyme hydrolysis of keratin is a safe method to use recalcitrant keratin by-products. *Bacillus* strains are the primary keratinolytic microorganism for keratin hydrolysis often reported in the literature [43]. The new strain used for keratin biodegradation at 30 °C is *Bacillus cereus* B5esz. The medium used comprises of $MgSO_4$, KH_2PO_4, $FeSO_4$, $CaCl_2$, yeast and keratin (*i.e.* chicken feathers or pig bristle) and is maintained at a pH of 7.1 before autoclaving [44]. Another *Bacillus* strain (*i.e. Bacillus subtilis* AMR) isolated from poultry waste was used in hair care products for the production of keratin peptides. Feathers with a limited volume of yeast were hydrolysed at pH 8.0 and 28 °C and extracted for five days [45]. Six non-pathogenic fungal strains (*Acremonium murorum, Aspergillus sidowii, Cladosporium cladosporoides, Purpureocillium lilacinum, Neurospora tetrasperma, and Westerdikella dispersa*) were isolated from alkaline soils and tested for their ability to produce keratinolytic enzymes. Strains were grown on feather meal agar and also in submerged cultures. The highest proteolytic and keratinolytic activities were found to be significantly associated with *P. lilacinum* [46].

P. lilacinum strain PL-HN-16 has the ability to degrade feathers. After a 3 day procedure, feather barbules fell off as they were weakened and partly deteriorated by a 54 % degradation rate, followed by complete degradation after four days [47]. Enzymatic methods for extraction of keratin nanoparticles have also been proposed. Savinase enzyme is used to extract keratin from wool and feather. Addition of anionic surfactant and sodium bisulfite increases the effectiveness of enzymatic methods [48]. Various microbial enzymes with degradation condition are listed in Table 1.

4.2. Dissolution in ionic liquids

Ionic liquids (ILs) are a category of ionised salts with a melting point below the boiling point of water. Ionic liquids are considered eco-friendly and safe solvents due to their non-volatile and durable characteristic, excellent chemical and thermal resilience, non-flammability and high solvation capacity. At the desired time and temperature, keratin materials are added in the ionic liquid with the regeneration of keratin fibres using water as a coagulation bath [49]. However, the cost of ILs is a significant constraint for its usage in the industrial extraction method of keratin. The ILs of imidazole possess greater extraction capacity and higher extraction levels, and the findings were best in 1-Butyl-3-imidazolium ion ($Bmim^+$), whereas the dissolution efficiency of quaternary ammonium and phosphonium was low [50]. Concerning anions, Cl^- demonstrated the best possible dissolving efficiency with higher extraction levels, and no dissolution was observed for BF_4^- and PF_6^- anions [51]. However, at least 65 % of the disulfide bond in keratin should be cleaved to achieve dissolution in ILs. The use of ionic liquids with this group helps in easy degradation by minimising the disulphide bridges like [bis-(2-Ethylhexyl)ammonium][thioglycolate] and [choline][thioglycolate]. However, [choline][thioglycolate] did not lead to an increase in solubility of feathers as compared to [Amim]Cl and [Bmim]Cl. Maximum extraction rate with thioglycolate-based ILs (51 %) was attained when a 1:20 liquor ratio was used at 130 °C for ten hours [52]. The various ionic liquids with additives, source and ionic liquid (solid-liquid ratio) with the experimental condition are presented in Table 2.

Table 1
Enzymatic and microbial method with degradation condition.

Microbial enzyme	Source or substrate	Degradation condition	References
Bacillus subtilis	CF (chicken feather)	40 °C and pH maintained for 7–11 days.	[113].
Bacillus subtilis DB 100 (p5.2)	CF	37 °C, 700 rpm agitation.	[114].
Kocuria rosea	CF	40 °C, a specific growth rate of 0.17 in a basal medium as a fermentation substrate.	[115].
Bacillus safensis LAU 13	CF	40 °C with pH 7.5, degraded CF after 6 days between 28 and 32 °C, At 50 °C with pH 8.0 optical activity.	[116].
Bacillus amyloliquefaciens 6B	CF	pH 8.0. and 50 °C completely degrade in 24 H.	[117].
Scopulariopsis brevicaulis, Trichophyton mentagrophytes	CF	The highest keratinase activity was estimated by *S. brevicaulis* (3.2 kU mL^{-1}) and *T. mentagrophytes* (2.7 kU mL^{-1}) in the culture medium shows 79% and 72.2% of degrading ability.	[118].
Vibrio sp. strain kr2	CF	pH ranging from 6.0 to 8.0, at 30 °C medium containing up to 60 g L^{-1} reaching maximum soluble protein values around 2.5 g L^{-1}.	[119].
Stenotrophomonas maltophilia BBE1-11	CF	pH 7.0–11.0, 40–50 °C for two days.	[120].
Stenotrophomonas maltophilia R13	CF	pH 7.0 at 30 °C, the maximum yield of the enzyme was 82.3 ± 1.0 Uml^{-1}.	[121].

4.3. Steam explosion process

Steam explosion (SE) is a hydrothermal procedure that utilises high-pressure saturated steam to heat biomass material quickly in a reactor. The biomass is maintained for brief intervals of 1–10 min until the vapour enters and disbands the substance at an acceptable temperature (180–230 °C). At the end of the treatment, the pressure is rapidly dropped, causing explosive decompression and rupturing of the biomass [53]. Keratin production through exploring chemical-free methods like a steam explosion technique was implemented in wool fibres. The wool fibres are processed at 220 °C with 10 min by saturated steam, which guarantees the dark-yellow band separation of the substantial component by a 120-mesh cut screen. The liquid is processed by centrifugation, sedimentation, and finally, the supernatant is retrieved [54]. The dissolved protein is extracted from the supernatant, is purified with acetone and then cleaned with distilled water. Flash steam-explosion is considered to be a safe and functional pre-treatment method to improve feather solubility in deionised water and solvents or buffers like potassium phosphate (PBS; 0.01 M, pH 7.5), as well as 2% urea and 0.2 % NaOH. During the pretreatment stage, the feathers were put in the chamber of the steam explosion unit at 1.4–2 MPa steam pressure for a duration of 0.5–5 min followed by explosive decompression within 0.1 s. The yield of extraction improved with a rise in the pressure of SFE treatment in all considered media. However, the impact of the pressure increase was more for PBS + Urea (2 %) buffer and NaOH (0.05 M) [55]. The impact of increased pressure on different buffers led to a greater yield in keratin extraction. The optimal condition with source and degradation property by steam explosion methods is described in Table 3.

4.4. Microwave irradiation process

Microwave technology has been widely developed over the last 20 years as a useful tool for chemical reactions. The benefit of this technology is the attainment of a more homogeneous heating process in less time. In this process, all polar molecules found in the reactor adsorb energy in microwave-assisted heating, thereby ensuring a rapid and homogeneous increase of temperature, with fewer reaction times resulting in predictable energy saving. Microwave irradiation was explored as a chemical-free process for the extraction of keratin from wool [56]. Microwave irradiation was applied to a sample of wool immersed in water for up to 60 min, with different temperatures and liquor ratios (150 °C & 1:5, 170 °C & 1:30 and 180 °C & 1:100). After

Table 2
Extraction of keratin protein using various ionic liquids.

Ionic liquid and additives	Substrate	Solid, liquid ratio	Temperature (°C) and time (H)	Solubility	References
[Bmim]Cl	Feather	1:2	130 & 10	50 %	
[Amim]Cl	Feather	1:2	130 & 10	50 %	[122].
Choline thioglycolate	Feather	1:2	130 & 10	45 %	
[Amim]Cl + 10 wt% Na_2SO_3	Feather	1:20	90 & 1	4.8 %	[18].
[Bmim]Cl + 10 wt% Na_2SO_3	Feather	1:20	90 & 1	4.8 %	[18].
[Bmim]Br + 10 wt% Na_2SO_3	Feather	1:20	90 & 1	4.2 %	[18].
[Bmim]NO_3 + 10 wt% Na_2SO_3	Feather	1:20	90 & 1	4.2 %	[18].
[Hmim]CF_3SO_3 + 10 wt% Na_2SO_3	Feather	1:20	90 & 1	0.2 %	[18].
[Bmim]HSO_4 + 10 wt% Na_2SO_3	Feather	1:20	90 & 1	4.1 %	[18].

Table 3
Extraction of keratin by steam explosion method with optimal conditions and properties.

Substrate	Optimal conditions			Properties	References
	Pressure (MPa)	Temperature (°C)	Time (min)		
Wool	0.2–0.6	164.2	2–8	Up to 80 % digestion yield, 50 % reduction in cystine content.	[54].
Feather	0–2.0	50	<3	93.2 % pepsin digestibility.	[123].
Feather	1.4–2.0	60	0.5–5	Yield of keratin 43 %	[123].
Feather	0.5–2.5	–	1	91% digestibility.	[55].
Feather	2.2	220	120	Arginine diminishes.	[124].

this, the yellowish-brown slurry was passed through 120 mesh to extract the liquid fraction which was again filtered at 0.65 μm and then freeze-dried to obtain a powder consisting of proteins, free amino acids and polypeptides. The extraction yield improved with a rise in temperature. The microwave-alkali method was also analysed for the extraction of proteins from feathers. The maximum extraction yield of 26.74 mg/mL was obtained using an input of 800 W with 0.5 M sodium hydroxide concentration with a liquor ratio of 1:50 for 10 min [57]. The microwave irradiation method with temperature, time and yield are described in Table 4.

4.5. Superheated water method

Keratin hydrolysis with superheated water consists of the treatment of biomass with water at different pressure and temperature conditions until the protein is broken into oligopeptides. Wool fibres were superheated at 170 °C with a pressure of 7 bar for 60 min, and the solution collected was washed thrice to extract solid substance. Superheated water treatment was often used for keratin extraction from feathers which were enclosed in a pressure cell with water at 20 mg/mL and kept in a pre-heated oven. The degree of dissolution depends on the temperature and time of treatment. Under these conditions, an extraction yield of approximately 95 % was attained, with a molar mass between 1 and 1.8 kDa [55]. The dissolution percentage concerning temperature and time is shown in the graph (Fig. 4).

Table 4
Microwave irradiation with process condition and yield.

Source	Process conditions	Yield	References
Wool	Microwave irradiation with 150–180 °C and 60 min.	60 %	[125].
Wool	Microwave superheated water at 180 W for 30 min.	31 %	[16].
Feather	Microwave at 160–200 °C for 20 min.	72 %	[126].

Keratin extraction by chemical hydrolysis (acid, base, catalyst) requires high temperature and pressure and poses a significant environmental risk. The chemical hydrolysis process causes emission of certain gases like CO and SO_2 into the environment which is responsible for causing cancer and various respiratory and cardiovascular diseases [58]. Although the hydrolysis is highly efficient, certain amino acids like tryptophan are lost in the process. The product obtained will have low nutritional value due to minor amounts of essential amino acids. Its solubility and stability are dependent on the rate of degradation of the protein. Thus, it is vital to develop smart and efficient biotechnological methods for keratin extraction, which are also environmental friendly.

In comparison to the chemical method; protein degradation for extraction with enzymes, ionic liquids, steam explosion, microwave irradiation, and superheated water extraction are considered green and eco-friendly methods. Extracting through dissolution in ionic liquids results in complete recovery of keratinous material and is also an eco-friendly approach. However, the high expenses limit its industrial usage. The enzymatic process is highly expensive with little guarantee pertaining to extraction yield. Lastly, the steam explosion, microwave and superheated water treatments require thermal energy and increased pressure and temperature conditions to destroy keratinous biomass and can have a severe environmental impact. Hence, it is necessary to develop economical, sustainable and eco-friendly methods of keratin extraction.

5. Application of valorised keratin

Keratin has a wide range of applications, and serious efforts have been put in the development of several methods involved in the extraction of keratin. Based on the type of application, keratin is extracted and designed in many forms like films, fibres, biomaterials, hydrogels, sponge and scaffold. Keratin is a protein with cysteine

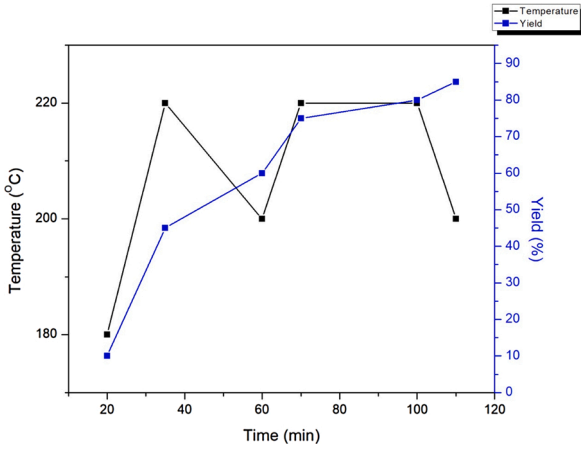

Fig. 4. Keratin extraction from superheated water treatment.

residues in high amounts that form the backbone of the polypeptide. This residue builds sulfur-sulfur bonds with another cysteine molecule to form disulphide bridges, *i.e.* cysteine-cysteine cross-linkage to give strength and stiffness to the keratin in solid state [59].

Importance of keratin in the various industrial sectors has been cited through many scientific works of literature. For decades keratin-based biomaterials have been used in biomedical application. Keratin based biomaterials along with other active ingredients such as growth factors, cellular extracts or pharmaceuticals, they can augment the wound healing cascade. Combination of these materials with tissue engineering techniques has resulted in many positive clinical outcomes [60]. The keratin-based biomaterials possess the intrinsic ability to self-assemble, are biocompatible and biodegradable and encourage cellular proliferation [61]. They are readily available in the global market. The incorporation of nanostructures with biopolymers has excellent potential and exhibits improved mechanical, thermal and barrier properties [62]. Bio-nanocomposites have gained attention because of their enhanced material properties with the aid of nano reinforcements. The two different nanoparticles, montmorillonite (MMT) and cellulose nanocrystals (CNCs), at 0%, 1%, 3%, 5%, and 10 % loading contents were studied as reinforcement materials in modified chicken feather keratin [63]. Keratin can become mainstream biomaterial in the future if its mechanical and physical properties are enhanced. Several approaches for modulating its properties have been considered including the addition of natural and synthetic polymers.

Based on the extraction method applied, the cysteine-containing proteins form keratoses during the oxidation process and kerateins during reduction and attributed to the presence of sulfur-containing groups in them [64]. Keratoses are hygroscopic, water-soluble, non-disulfide cross-linkable, and are prone to hydrolytic deterioration at extreme pH, mainly due to polarisation of cysteic acid groups [65]. Hydrolytic degradation leads to faster degradation of keratoses *in vivo*. Contrarily, kerateins exhibit low polarity and low solubility in water, but they possess more stability at extreme pH conditions. Kerateins undergo oxidative coupling by re-crosslinking of cysteine groups which causes the biomaterials to survive *in vivo* conditions from weeks to months [66].

The strong foundation for the expansion of keratin containing biomaterials is due to its unique physical, chemical and biological aspects. Since 1972, keratin has been used in various forms such as gels, films and scaffolds [67]. The primary research using keratin-based biomaterial was carried out when vascular grafts coated with keratin were placed in dogs for over 200 days without incidence of thrombosis [68]. Since then, keratin is being used as a biomaterial in bone regeneration, hemostasis, nerve repair and wound healing [69]. Keratin biomaterials have cell-binding motifs like leucine-aspartic acid valine (LDV) and glutamic acid serine (EDS) which are responsible for cellular proliferation [61]. Keratins are even trusted to participate in controlling functions to mediate cellular performance like other intermediate filaments [70]. Thus, these biological activities in keratin-based biomaterials can prove to be a beneficial role in tissue engineering applications (Fig. 5).

5.1. Keratin in hydrogel

Hydrogels are hydrophilic polymers in chain network held by inherent crosslinking of individual polymer chains [71]. Hydrogels have a high water-absorbing capacity and are widely used as materials for contact lenses, matrices for cell encapsulation, protein separation mediums, and devices for the controlled release of drugs and proteins [72].

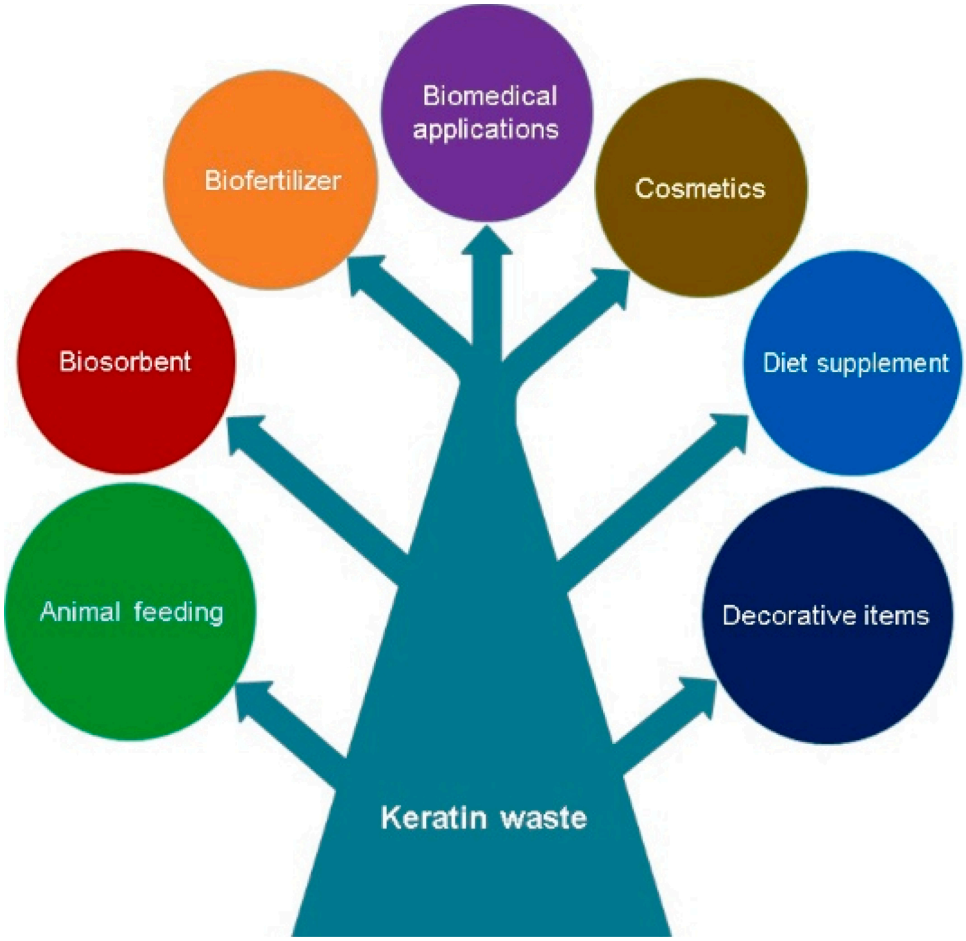

Fig. 5. Various applications of keratin waste.

The three-dimensional design helps in the release of molecules like antibodies, drugs, and proteins in a controlled manner.

Hydrogels are also known as reversible or physical gels. They play an essential role in forming a network by molecular chains involving ionic and hydrophobic forces or hydrogen bonding. Physical gels are often reversible and can easily be dissolved by altering pH, temperature and ionic strength of the solution. On the other hand, in permanent or chemical gels, covalent bond networks are formed with different macromolecular chains by crosslinking polymers in a dry state or solution [73]. Depending upon the functional groups present in their structure, the permanent gel can be charged or uncharged. The charged hydrogels show changes in swelling with pH change, and fluctuations in shape are noted upon exposure to an electric field [74]. For 50 years, hydrogels have established a significant position and have a wide range of applications [75]. In recent times, hydrogels turned out to be two or multiphase systems with polymer chains in the 3-dimensional network in which water fills the space between macromolecules.

The neuro inductive nature of keratin hydrogels and the proficiency of helping in rejuvenating peripheral nerve injury were described in a mice model [76]. In detail, the keratin gel channels serve as neuro-inductive provisional matrix-mediated axon regenerators with efficient retrieval when compared to sensory nerve autografts. In another study, peripheral nerve regeneration concerning time course was evaluated by neuromuscular recovery and nerve histomorphometry. Hydrogels containing keratin claimed to accelerate nerve regeneration by improving electrophysiological recovery and also by increasing axon density at initial time points. Keratin hydrogen proved useful as a hemostatic agent in a rabbit model of lethal liver injury. The keratin gel also helped in recovery at the injury site by initiating the formation of thrombus and by making an outer cover at the wound spot allowing cellular infiltration and granulose tissue formation [77]. Barati et al. stated that keratin hydrogels are capable of controllable degradation and can be used for encapsulation and stem cells delivery in tissue regeneration [78].

5.2. Keratin in films

Thin layers of a constituent exhibiting great flexibility and massive coverage are known as films. Keratin solution can self-assemble to form a thin film [79] and useful in drug delivery application. The cell attachment and proliferation were enhanced. In general, pure keratin film is fragile and brittle. Various methods, like the addition of plasticisers (ethylene glycol, glycerol, sorbitol) and crosslinking agents, are suggested in the literature to overcome this issue. The film's combination with natural [80] or synthetic polymers forming a matrix is recommended to improve keratin's mechanical properties.

Based on wound type, suitable dressing material must be applied. Materials used for wound dressing should allow angiogenesis and synthesis of connective tissue. Protein-based films tend to absorb the treatment drug and minimise the risk of contamination from multiple treatments. There are several procedures to produce keratin films like compress moulding, electron spinning, solvent casting, thermal pressing and layer by layer deposition [81]. Keratin based films are preowned for tissue engineering applications. Solvent casting is a standard method for the production of high-quality thin films [82]. This process enables the production of thin films with uniform thickness and utmost optical purity and is technically convenient. The pure form of keratin films have less mechanical strength; the addition of glycerol produces transparent films with higher mechanical strength and flexibility and decomposable in *in vitro* as well as *in vivo* [83].

Chitosan is a biomolecule that possesses higher biocompatibility and biological function in wound healing and exhibits antibacterial activity. The addition of chitosan into keratin resulted in robust and adaptable films with enhanced protuberance. Furthermore, the multifaceted films were shown to be a proper substrate for cell culture of mammals. Alternative fabrication technique can be attained for mechanical reinforcement. S-sulpho keratin powder was used by compression moulding for preparing films [84]. The mechanical properties of films can be modulated by regulating the moulding temperature and water content.

Keratins extracted by reduction method and the films processed by solvent evaporation were appropriate for penetration with regards to its mechanical stability and water repellent property. The combination of keratin with ceramides was used for the progress of membranes to mimic the stratum corneum [85]. Keratin was modified with cell adhesion peptides, Arg-Gly-Asp-Ser (RGDS) at the free residues of cysteine. The keratin films with RGDS evidenced to be an excellent mammalian substrate for cell growth and exhibited the capability and versatility of keratin biomaterials [61]. The keratin-based films were preowned for ocular surface reconstruction, where the amniotic membrane of humans is utilised as the keratin films. These films are translucent and stronger than amniotic membrane with the same levels of corneal epithelial cell attachment and proliferation, which signify the standby of amniotic membrane in ophthalmology.

5.3. Keratin in electrospinning nano fibres

Keratin with the characteristic microstructural property is used in composites and non-woven fabrics. Over the years, biocompatible polymeric nanofibers obtained by electrospinning have gained importance in biomedical applications. Electrospinning is a technique in which high voltage is used to generate a charged jet of polymers drawn towards collection plate [86]. The non-woven fibrous material is segregated in nano to microscale range. Improved physical properties like smaller pore size, higher porosity, three-dimensional features, and higher surface-area-to-volume ratio can benefit growth and cell adhesion [87]. These electrospun nanofibrous membranes have found their way into dressings for wound healing and scaffolds for tissue engineering [88].

The electrospinning process for harvesting keratin from hair and wool fibres has also been delayed due to the intrinsically weak mechanical properties of pure keratin protein. However, keratin's ability to form fibres is improved by incorporating synthetic or natural polymers. Keratin fibres are prepared by mixing keratin and polyethene oxide (PEO) powder with the weight ratio of 50:50 in aqueous solution, also with 7 % and 10 % of total polymer concentration to counter the electrospinning constraints and create perfect fibrous material [89]. Electrospinning tends to weaken the self-assembly characteristic of keratin resulting in low complex conformation of the protein. This phenomenon is not observed in spectroscopic and thermal analyses. Fibres with different concentration of keratin and PEO were produced. The instability of water and low mechanical properties restricted the use of nanofibrous keratin/PEO mats [90]. Much research is being carried out to enhance the physical properties of keratin.

5.4. Keratin in sponges and scaffolds

The capability of keratin protein to polymerise and self-assemble into the three-dimensional structure has governed its progress as scaffolds. The scaffold materials assist cell adhesion, proliferation and differentiation. The most common technique for keratin bio-composite generation is by freeze-drying the keratin solution. The sponge scaffolds were produced after controlled freezing by lyophilisation of an aqueous keratin solution, sponges with homogenous porous microstructures were thus formed [79]. The pH and concentration of cross-linkers, plasticisers, natural and synthetic polymers in the keratin matrix may influence the film-like porous composite structure. The faster cooling/freezing rate of the keratin solution during the sublimation process can influence the size of pores and ice crystal formation.

Long term cell cultivation of wool keratin scaffolds was first reported by Tachibana et al. in 2001 [91]. These scaffolds were developed by lyophilisation of aqueous wool keratin solution after controlled freezing, giving rise to a rigid and heat-stable structure with a homogeneous porous microarchitecture. This keratin includes RGD and LDV cell

Table 5
Various forms of keratin with composition and its biomedical applications.

Source	Composition	Application	References
Keratin hydrogel	15 % (*w/v*) hydrogel	Early cellular response to sciatic nerve injury in a rat model.	[127].
Keratin hydrogel	5% PVA, 5% keratin.	Wound healing process *in vivo*.	[128].
Keratin hydrogel	9% gel.	Skin regeneration after burns.	[129].
Keratin hydrogel	3% glycerol to make a 20 % (*w/v*) solution that is cytocompatibility equivalent to collagen hydrogel.	Pulp-tissue engineering enhanced,odontoblast cell behavior.	[130].
Keratin hydrogel	15 % gel.	Rapid regeneration of peripheral nerves.	[131].
Keratin hydrogel	20 % (weight per volume, *w/v*) hydrogels.	Drug release over 3 weeks.	[132].
Keratin hydrogel	15 % keratin hydrogel.	Nerve regeneration (Neuromuscular recovery with keratin higher than with empty conduits.	[133].
Keratin hydrogel	Lyophilized material with PBS at a 15 % *(w/v)* concentration.	Keratin neuro conduit contains regulatory molecules capable of enhancing nerve tissue regeneration by inductive mechanisms.	[133].
Keratin film	The film doped with different amounts of methylene blue.	Tissue engineering wound healing, antimicrobial photodynamic activity upon irradiation with visible light support for photodynamic therapy treatment.	[134].
Keratin film with transglutaminase (TG)	Treatment with TGase (30 Ug^{-1} keratin) for 18H at 40 °C.	Films with improved stability in PBS and artificial gastric juice. Films with a lower drug release rate.	[135].
Keratin/ gelatin film	10 % keratin + 10 % gelatin +1 ml, ethylene glycol +0.35 ml glutaraldehyde.	Wound dressing materials.	[136].
Keratin–chitosan film	10–30 % chitosan, 20 % glycerol in 75 % acetic acid.	Contact lens material.	[137].
Keratin film	Shindai keratin + glycerol dried in a ventilated oven at 50 °C for 24H	Drug release (Rhodamine B).	[138].
Keratin–HA films	Glycerol, 40 % HA, 6% protein, treated with ammonium thioglucolate.	Full integration into the bone by 12 Weeks.	[139].
Keratin polyamide 6 film	Polyamide 6, electrospinning.	Keratin improves the miscibility and hydrophilicity of the film.	[140].
Keratin film	Glycerol used as a plasticiser, 160 °C for 2–8 min.	Good physical properties.	[141].
Keratin based scaffold	Keratin–chitosan 2 : 1 (*w/w*), (200 mg of chitosan, 15 ml of 75% acetic acid, 10 ml of keratin solution) Frozen at −80 °C.	Antibacterial properties	[142].
PLA/chitosan/Keratin composites	A111: 70 % PLA and 30 % chitosan; A121: 68 % PLA, 30 % chitosan and 2% keratin; A131: 66 % PLA, 30 % chitosan and 4% keratin.	Support osteoblast attachment and proliferation during short-term culture.	[143].
Keratin sponge with hydroxyapatite(HA)	Calcium and phosphate precipitated in sponge and HA by trapping inside the keratin sponge matrix.	Positively affect and alter the differentiation pattern of the osteoblast cells.	[144].
Keratin-HA (hydroxyapatite)	Hydroxyapatite (HA) with 70 % keratin.	Cells had better viability with HA in Keratin matrix.	[145].
Carboxymethylated functionalised keratin	With hydroxyapatite.	Used for bone healing and bone drug delivery.	[146].
Keratin-Chitosan	Keratin–chitosin (2:1).	Better mechanical property. Used in wound healing and artificial skin substituent.	[147, 142].
Keratin with chitosan/ starch matrix	Keratin 20 % dispersed on the chitosan matrix.	Good biocompatibility.	[148].
Keratin- Agar and keratin-Alginate	Agar and alginate beads blende with keratin solution by leaching and lyophilisation method showed porosity with 94 and 98 %.	Improved mechanical property.	[149, 150].
Keratin Fibre Keratin with polymer	(Hydroxybutyrate hydroxy valerate) PHBV fibre and Poly(L-lactic acid).	Wound dressing materials.	[151].
PCL/keratin fibre	PCL(Polycaprolactone)/keratin (7 : 3) with the addition of hydroxyapatite particles	Bone tissue engineering.	[152].
keratin/PLA	3D (Three-dimensional) ultrafine fibrous using electrospun.	Mesenchymal stem cells proliferation.	[152].
Keratin-Polyamide 6 composite	Fibroin solutions dissolved in 15 % *w/w* formic acid and film regenerated from the water with stirring for 2 h at room temperature.	Biomedical devices, textile fibers, water filtration.	[153].
Keratin as biosorbent	Modified chicken feather with ethylenediamine and epichlorohydrin cross-linker	Removal of Cr(VI) ions.	[154].
Biosorbent	Poly (N- isopolypropylacrylamide) (PNIPAM) with chicken feather.	Removal of Arsenic species.	[155].
Keratin bio sorbent	keratin with polyhedral oligomeric silsesquioxanes (POSS) nanocages and goethite dopant.	Removal of naphthenic acids (NAs) from oil sands process affected water (OSPW).	[155].
Chicken feather	Keratinolytic enzymes and actinomyces are produced by bacteria which degrade keratin waste biomass.	Used in composting.	[156].
Chicken feather	Feather treated with *corynebacterium spp*	Hydrolyse feather fertiliser used for the banana plant. For root or shoot dose for cultivating other crops.	[112].
Chicken feather	Thermophilic actinomycetes strain used	Fertiliser for ryegrass cultivation.	[157]
Feather keratin peptide	Enzymatic hydrolysis of keratinases using *Bacillus subtilis* AMR	Used for hair care products.	[45]
Keratin protein for cosmetics	Keratin 25 obtained from human hair and wool Improves hydration and elasticity of skin and hair.	Skin and hair moisturiser, firming agent, Hair shiner.	[158]
Hydrolysed keratin peptide	Hydrolysed keratin prepared from wool tested on the skin with aqueous and internal wool lipids(IWL)liposome suspension.	Improves hydration and elasticity of healthy skin.	[159]

adhesion sequences, has excellent cell stability. It assisted in fibroblast attachment and proliferation for 23–43 days. The diameter and interconnectivity of the scaffold pores are vital for obtaining suitable cellular infiltration and nutrient delivery. Through the compression-moulded/particulate leaching (CM/PL) technique, the fixed pore size and porosity were produced with S-sulfo keratin sponges. The resulting sponges had enough mechanical and water-insoluble properties [84].

It has been discovered that the presence of free residues of cysteine within the scaffold has potential modification sites for bioactive substance immobilisation. The chemical treatments can develop this functionalisation in keratin sponges with iodoacetic acid, 2-bromo ethylamine and iodoacetamide to give carboxyl, amino and amide sponges respectively. Chemically modified keratin sponges resemble ECM proteins and hybridise with bioactive molecules in the presence of active groups. The hybridisation of keratin sponges with calcium and phosphate is obtained by chemical binding. The hybridised sponges assisted the production of osteoblasts and modified their differentiation pattern [82]. Keratin carboxyl sponges have also been put into use with bone morphogenetic protein-2 (BMP-2) which resulted in pre-osteoblasts differentiation and growth [92].

Keratin composites prepared without any additives tend to have a rigid structure that restricts its application in tissue engineering. Hence, keratin matrix reinforcement by the combination of different substituents like natural and synthetic polymers has resulted in improved mechanical properties. For instance, chitosan a natural polysaccharide is reinforced with the keratin matrix. Chitosan is known for its biodegradability, biocompatibility, non-toxicity and antimicrobial properties which make it a favourable candidate for biomaterials [93]. By changing the viscoelastic properties of keratin, it can be used as scaffolds for tissue engineering [94]. The hydrogel scaffolds prepared using chicken feather keratin exhibit high cell proliferation rate in tissues for wound healing [95] (Table 5).

5.5. Keratin as biosorbent for removal of heavy metals from wastewater

Water being the universal solvent, is highly vulnerable to pollution. Every year chemical wastes from chemical industries are disposed of in large quantities into rivers and lakes. If appropriate and effective wastewater-treatment methods are not applied, it can lead to severe water pollution [96]. Wastewater discharged from chemical industries comprises of chemical waste in the form of heavy metals and its complexes which are dangerous to human and aquatic life. For instance, Arsenic (As) in the form of arsenite (AsO_3) and arsenate (AsO_4) is toxic. The contamination is due to fossil fuel production, metallurgical mining, smelting and rock sediments. The higher concentration of arsenic disrupts the cardiovascular function, causes bone marrow depression, liver tumour and visceral cancer. Whereas, Cadmium (Cd) is the most carcinogenic metal manufactured during mining, electroplating and smelting.

Accumulation of Cd beyond acceptable limits leads to cancer, hypertension and weight loss. Chromium (Cr) is also released from the industrial effluents in its untreated form, which is highly carcinogenic [97]. Copper (Cu) from the electronic industry is left to accumulate in the water. When it comes in contact with the human body, it results in insomnia, liver damage, lung cancer and neurotoxicity. Lead (Pb) in I and II oxidation states from battery, electroplating and pigment industries causes anaemia, brain damage, loss of appetite, nausea and vomiting. Nickel (Ni) generated from electroplating, steam electric power plants and mineral processing industries cause chronic asthma and lung cancer. Mercury in its oxidative state (I and II) forms many ionic compounds and complexes with other substances in wastewater. It is hazardous to the nervous, renal and circulatory systems. Zinc (Zn) from mining and manufacturing industries lead to diarrhea, distress and nausea. Over the years, various wastewater treatment methods have been used to remove heavy metals and to purify water.

Biopolymers have benefits in green chemistry with their prominent role in averting ecological pollution. Application of keratin can be a promising technology for the refinement of metal contaminated natural and wastewater resources. The functional groups in keratin protein, namely carbonyl, carboxyl, hydroxyl and sulfhydryl, play a crucial role in biosorption of pollutants. The hydrophobic interactions found in biosorbents is due to organic and bacterial species in wastewater. It involves energy interaction and electron transfer in protein by using DLVO theory [98].

Water pollution is one of the major global risk factors for illness and death. Heavy metal ions are harmful contaminants, and their presence in aquatic ecosystems pose a severe threat to aquatic biodiversity and drinking of contaminated water is hazardous for humans. Accumulation of heavy metal ions beyond permissible limits is dangerous for human as well as aquatic life [99]. There is a risk for long-term contamination in biological systems, even if the concentration of heavy metals is below its limits [2]. Many wastewater treatment technologies have restrictions for sludge handling and its safe disposal, which is suitable only for high metal concentrations. However, conventional water treatment techniques require complex operational system, are relatively expensive and are metal specific. Hence, in recent times, the use of biopolymer for heavy metal removal has gained popularity [100]. By using keratin wool, numerous metals such as aluminium, copper, cadmium, lead, mercury, chromium and silver were separated. In another study by Mohair, keratin was used to remove copper from aqueous stream [101].

The oxy-anionic contaminants of selenium and arsenic were removed by high sorption of water uptake at lower pH, which was obtained by modification of keratin, as conveyed by Nicomel et al. [102]. Keratin extracted from three different sources like chicken feathers, human hair and animal horns were prepared and composed as biosorbents. The extracted keratin was examined and compared by Fawzi Banat et al. for Zn(II) and Cu(II) ions removal from water. However, higher sorption efficiency was found in animal horn than chicken feathers and human hair. Keratin from chicken feathers was used as biosorbent by the same group, and its properties were enhanced by chemical treatment with NaOH and anionic surfactant dodecyl sulphate (SDS) for Cu(II) and Zn (II) removal from wastewater [103].

5.6. Application of keratin as active ingredient in cosmetic products

Keratin compounds can be used for skin and human hair as cosmetics. It is added as a cosmetic blend with other natural polymers like chitosan, collagen and silk fibroin [104]. Keratin tends to retain moisture as it comes in contact with stratum corneum in the skin and hair cuticle. Hydrolysed keratin is used as a cosmetic ingredient that enhances skin hydration and flexibility [105]. Skin layer or film set up by keratin molecule provides a smooth and soft feeling [106]. Keratin is an essential ingredient in shampoos and conditioners, hair loss concealing products and other products used as hair accessories [107]. Strengthening of the hair fibres and lowering fibre breakages for hair was developed by keratin hydrolysates [107]. Keratin is also used as a toner for uniform hair colour retention and in hair shading splashes. Protein hydrolysates are added in hair care products to repair damaged hair [108].

5.7. Keratin as biofertiliser

Organic fertilisers were prepared by sulfur bound amino acid solution as growth enhancers for plants [109]. Sheep wool represents a 100 % natural biodegradable material that does not produce any toxic substances or pollutants in the soil or nearby environment. Hence it is considered as a natural fertiliser which is suitable for protecting the biodiversity for flora and fauna. Wool fibres magnify in humid conditions, and by aerating the soil, they benefit the plant roots. The nutrient released will be efficient and will minimise re-fertilisation throughout the season. This is due to the superior absorption and water retention

capacity of sheep wool that prevents drying of the soil and reduces erosion. Keratin is a reliable source of nitrogen which is used to prepare fertilisers [110]. Keratinolytic enzymes are produced by bacteria and fungi and cause degradation of waste biomass of keratin. *Bacillus* genes generate sufficient keratinolytic enzymes, and actinomycetes also contribute to the degradation of keratin [111]. Sheep wool and feather have around 90 % keratin and are used in composting. Feather waste is rich in peptides, amino acids and minerals, and makes a good bio-fertiliser. The feather hydrolysate has the potential to restore contaminated soil and accelerate plant growth and has been found to be effective in cultivation of banana and other crops [112].

6. Future perspectives

Poultry processing industries are paying huge costs for the disposal of their feather waste as there is limited landfill space. Numerous efforts have been put in the development of green methods for keratin extraction. However, there is still a need to lower the usage of chemicals or replace them with biodegradable and eco-friendly biomaterials. The sustainability of poultry-processing plants is threatened, and the challenge is to design technologies that convert waste on-site into valuable products which can be used on-site or sold. It is crucial to develop effective and eco-friendly techniques of valorisation. There is still much research to be explored in the utilisation of chicken feathers for beneficial use. Keratin also used in electronic industries with graphene nanoplatelet (GnPs)-based conductive ink.

7. Conclusion

Various methods to valorise the keratinous waste have been described by ionic liquid dissolution, enzymatic hydrolysis, steam explosion and microwave irradiation were reviewed in detail. Out of all the extraction method, the ionic liquids can be considered as a green method as it is completely recovered and can be reused after the extraction process. It is clearly shown by the previous researcher that keratin can work as a bioabsorption agent for different water pollutants. Further research need to be carried out to set up green, cost-effective and less energy-intensive extraction procedures with reproducible physico-chemical properties. Despite a few efforts documented to utilise this valuable waste by different countries, enormous scope remains in Malaysia to undertake any project for the transformation of this substantial biological waste into useful products. Thus, keratin valorisation-based technology will help to convert the keratin waste to useful products along with the reduction of cost for waste management.

Declaration of Competing Interest

The authors report no declarations of interest.

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