



Preparation and Characterization of Soluble Gelatin from Chicken Skin for Food and Pharmaceutical Applications as an Ecofriendly Sustainable Alternative: A Review of Literature

Teklay Asgedom Teferi^{1*}, Hailemariam Tesfay Gidey², Bisrat Tesfamichael Mekoya³, Eskindir Yesuwerk Ayle⁴

¹Manufacturing Industry Development Institute Leather (MIDI); Leather and Leather Products Industry Research Development Center (LLPIRDC), Addis Ababa, P.O. Box 5, Code 1058, Ethiopia. Email: teferitwoasgedom@yahoo.com

²Manufacturing Industry Development Institute Leather (MIDI); Leather and Leather Products Industry Research Development Center (LLPIRDC), Addis Ababa, P.O. Box 5, Code 1058, Ethiopia. Email: Hailishtes7@gmail.com

³Manufacturing Industry Development Institute Leather (MIDI); Leather and Leather Products Industry Research Development Center (LLPIRDC), Addis Ababa, P.O. Box 5, Code 1058, Ethiopia. Email: Luie347@gmail.com

⁴Manufacturing Industry Development Institute Leather (MIDI); Leather and Leather Products Industry Research Development Center (LLPIRDC), Addis Ababa, P.O. Box 5, Code 1058, Ethiopia. Email: eskaayy123@gmail.com.

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***Corresponding author:** Teklay Asgedom Teferi, Manufacturing Industry Development Institute Leather (MIDI); Leather and Leather Products Industry Research Development Center (LLPIRDC), Addis Ababa, P.O. Box 5, Code 1058, Ethiopia. Email: teferitwoasgedom@yahoo.com.

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Abstract

Traditional commercial gelatins, primarily derived from mammalian sources like bovine and porcine hides or bones, face growing constraints due to dietary restrictions, religious compliance (Halal and Kosher), and disease transmission concerns. Concurrently, large quantities of poultry processing by-products, specifically chicken skin, are discarded daily, posing an environmental burden. This review synthesizes current literature on the extraction, optimization, and characterization of soluble gelatin isolated from chicken skin. It critically examines various acid, alkaline, and enzymatic extraction methods that influence the yields and molecular properties of poultry-derived collagen. Key physicochemical parameters are evaluated, including amino acid profiling (high proline and hydroxyproline content), rheological behaviors, thermal stability, solubility, and gel strength (Bloom value). Furthermore, the review outlines the structural capabilities of chicken skin gelatin in bioactive encapsulation, film-forming applications, pharmaceutical capsule formulation, and food texture stabilization. Utilizing chicken skin as an alternative biomass provides an effective, sustainable, and eco-friendly biopolymer solution that promotes a circular economy while matching or exceeding key functional properties of mammalian gelatins.

Keywords: Chicken skin gelatin, soluble gelatin, biomass valorization, gel strength. Food packaging, encapsulation, sustainable biopolymers, circular economy

1. Introduction

The global poultry industry has experienced unprecedented growth over the past decades, with worldwide poultry meat production rising from 92.68 million metric tonnes to over 127 million metric tonnes annually (Alipal et al., 2021). This remarkable expansion, while addressing the protein demands of a growing global population, has simultaneously generated enormous volumes of processing by-products and slaughter wastes, including skin, feathers, feet, heads, and viscera. Poultry slaughter wastes are estimated to account for approximately 7–8% of live body weight, with cut components such as skin, feathers, offal, heads, blood, tracheae, and feet collectively contributing to roughly 9.5 million tons of underutilized protein-rich biomass each year (Talha et al., 2024).

Conventional disposal methods including incineration, composting, and rendering have been associated with significant environmental burdens, including greenhouse gas emissions, air and water pollution, and eutrophication (Talha et al., 2024). Consequently, the valorization of poultry waste through the extraction of high-value structural proteins has emerged as a critical strategy for advancing environmental sustainability and circular economy principles within the food and bioprocessing sectors. Gelatin, a thermally reversible hydrocolloid derived from the partial hydrolysis of collagen, represents one of the most functionally versatile biopolymers utilized across food, pharmaceutical, cosmetic, and biomedical industries (Gómez-Guillén et al., 2011). Its unique physicochemical attributes, including thermo-reversible gelation, film-forming capacity, emulsifying behavior, and water-binding properties, render it indispensable as a gelling agent, stabilizer, thickener, and encapsulating material (Haslindawaty et al., 2025).

In the food industry, gelatin is employed in confectionery, dairy products, meat formulations, and beverage clarification, while in the pharmaceutical sector, it serves as a primary constituent of hard and soft gelatin capsules, tablet binders, wound dressings, and plasma expanders (Mikhailov, 2023). Traditionally, commercial gelatin has been sourced predominantly from mammalian tissues, specifically porcine skins (46% of global output), bovine hides (29.4%), and bovine bones (23.1%) (Talha et al., 2024). However, reliance on mammalian raw materials is increasingly constrained by several compounding factors. The emergence of bovine spongiform encephalopathy (BSE) and concerns regarding transmissible spongiform encephalopathies have raised significant safety apprehensions surrounding bovine-derived gelatin (Talha et al., 2024). Furthermore, porcine-derived gelatin is prohibited under Islamic (halal) and Jewish (kosher) dietary laws, thereby excluding its consumption by more than one-third of the global population (Talha et al., 2024; Haslindawaty et al., 2025).

These limitations have catalyzed intensive research into alternative, non-mammalian sources of gelatin that are both safe and culturally acceptable. Among the various alternative sources, poultry by-products, particularly skin, have attracted considerable scientific attention as a promising substrate for gelatin extraction. Poultry skin is rich in collagenous connective tissue, with collagen constituting approximately 20–30% of the total animal protein content and being abundant in skin, tendons, cartilage, and bones (Haslindawaty et al., 2025). The conversion of poultry skin collagen into soluble gelatin through controlled acid, alkaline, or enzymatic hydrolysis offers a dual advantage: it mitigates the environmental impact of waste accumulation while yielding a functional biopolymer with properties comparable, and in certain respects superior, to those of mammalian gelatin (Talha et al., 2024).

Recent investigations have demonstrated that gelatin extracted from chicken skin, feet, and head blends exhibits high bloom values, favorable rheological profiles, and characteristic amide bands (amide A, B, I, II, and III) as confirmed by Fourier Transform Infrared (FTIR) spectroscopy, indicating structural integrity and functional viability (Bhargavi et al., 2025). Moreover, ultrasound-assisted extraction methodologies have been shown to enhance gelatin yield, gel clarity, textural parameters, and functional properties while significantly reducing processing time and eliminating the need for harsh alkali pretreatment (Bhargavi et

al., 2025). The characterization of poultry-derived gelatin encompasses a comprehensive suite of physicochemical, structural, thermal, and functional analyses. Proximate composition (moisture, protein, fat, and ash content), pH, and color parameters provide fundamental quality indicators, while advanced techniques such as FTIR spectroscopy, differential scanning calorimetry (DSC), SDS-PAGE, and matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry elucidate molecular structure, secondary conformation, and polypeptide chain composition (Esmacili-Kaliji et al., 2025; Bhargavi et al., 2025).

Rheological characterization, including the determination of storage modulus (G'), loss modulus (G''), gel strength (Bloom value), and viscosity, offers critical insights into the viscoelastic behavior and network-forming capacity of gelatin gels, which are directly correlated with their industrial applicability (Bhargavi et al., 2025). The functional attributes of poultry skin gelatin position it as a viable candidate for diverse applications within the food and pharmaceutical domains. In food systems, it serves as a stabilizing, emulsifying, and texturizing agent, with potential utility in edible films and coatings that extend shelf life and reduce microbial contamination (Haslindawaty et al., 2025). In pharmaceutical formulations, its biocompatibility, biodegradability, and film-forming properties render it suitable for soft and rigid capsule shells, drug delivery matrices, and wound healing hydrogels (Mikhailov, 2023). The alignment of poultry-derived gelatin with halal and kosher dietary requirements further expands its market accessibility and commercial potential (Talha et al., 2024).

Despite the growing body of literature on poultry waste valorization, a comprehensive, integrative review that systematically synthesizes the preparation protocols, characterization methodologies, functional properties, and application potential of soluble gelatin specifically derived from poultry skin remains limited. Existing studies have largely focused on individual extraction parameters or isolated functional assessments, without providing a holistic appraisal of the field. Furthermore, the comparative evaluation of poultry skin gelatin against conventional mammalian and other alternative sources, alongside an examination of sustainable extraction technologies, warrants critical scholarly attention.

2. Objectives of the Review

In light of the aforementioned context, this review aims to achieve the following objectives:

- To systematically review and synthesize the existing literature on the preparation and extraction of soluble gelatin from poultry skin waste, encompassing conventional (acid, alkaline, enzymatic) and emerging (ultrasound-assisted, microwave-assisted) methodologies, with particular emphasis on process optimization and yield enhancement.
- To critically evaluate the physicochemical, structural, thermal, and rheological characterization of poultry skin gelatin, including proximate composition, molecular weight distribution, FTIR spectral properties, amino acid profiling, gel strength, and viscoelastic behavior, in comparison with mammalian and other alternative gelatin sources.
- To assess the functional properties and techno-functional performance of poultry skin gelatin,

including its gelling, emulsifying, foaming, water-binding, and film-forming capacities, as indicators of its suitability for industrial applications.

- To explore and delineate the potential applications of poultry skin gelatin within the food industry (e.g., confectionery, dairy, meat products, and edible coatings) and the pharmaceutical sector (e.g., capsule shells, drug delivery systems, wound dressings, and tissue engineering scaffolds).
- To evaluate the sustainability, economic viability, and circular economy implications of utilizing poultry skin waste for gelatin production, including environmental impact mitigation, waste reduction, and alignment with halal and kosher dietary standards.
- To identify existing research gaps, technological limitations, and future research directions that will advance the commercialization and regulatory acceptance of poultry skin gelatin as an eco-friendly, sustainable alternative to conventional mammalian gelatin.

2. Methodology

2.1. Search Strategy

A systematic literature search was conducted across Scopus, Web of Science, PubMed, and Google Scholar using combinations of keywords: "poultry skin gelatin," "avian gelatin extraction," "soluble gelatin," "poultry waste valorization," "food-grade gelatin," "pharmaceutical gelatin," and "sustainable collagen." The search was restricted to peer-reviewed articles, reviews, and book chapters published in English between 2014 and 2025, with no geographical restrictions. Reference lists of identified articles were manually screened for additional relevant studies (snowballing).

2.2. Selection Criteria

Inclusion: Studies reporting extraction, physicochemical characterization, functional properties, or application of gelatin derived from poultry skin (chicken, turkey, duck, or other avian species) for food, pharmaceutical, or biomedical uses.

Exclusion: Studies on mammalian (porcine/bovine) or marine gelatin unless used for direct comparative analysis; non-soluble or non-food-grade industrial applications; conference abstracts, editorials, and non-peer-reviewed sources.

2.3. Screening and Data Extraction

Titles and abstracts were initially screened for relevance, followed by full-text assessment of shortlisted articles. Extracted data included (i) raw material source and pre-treatment; (ii) extraction methodology (acid/alkali/enzymatic hydrolysis, temperature, pH, and time); (iii) yield and recovery rates; (iv) characterization techniques (SDS-PAGE, FTIR, XRD, DSC/TGA, and amino acid analysis); (v) functional properties (gel strength, viscosity, emulsification, and film-forming capacity); and (vi) demonstrated food or pharmaceutical applications.

2.4. Quality Assessment and Synthesis

Selected studies were evaluated for methodological rigor, reproducibility, and relevance to sustainability claims. Data were synthesized narratively and grouped by (a) extraction and purification protocols, (b) structural and physicochemical characterization, (c) functional performance relative to commercial mammalian gelatin, and (d) specific food and pharmaceutical

applications. Critical gaps, scalability challenges, and regulatory considerations were identified to highlight future research directions and commercial viability.

3. Literature review

3.1. Preparation Methods

3.1.1. Pre-treatment: This stage removes non-collagen proteins and fats using dilute acid (e.g., HCl) or alkali (e.g., NaOH) solutions. Zhou and Regenstien (2005) demonstrated that alkaline and acid pretreatments effectively remove non-collagenous proteins with minimum collagen loss while also inhibiting endogenous protease activity that could otherwise degrade the collagen structure. Sarbon et al. (2013) applied a combined alkali-acid sequence (0.15% NaOH followed by 0.15% H₂SO₄ and 0.7% citric acid) to chicken skin, repeating each cycle three times to solubilize non-collagenous material and partially denature the collagen matrix prior to hot-water extraction. Enzyme-assisted methods can markedly accelerate this phase; Ahmad et al. (2017) reviewed how proteolytic enzymes such as papain and bromelain cleave collagen cross-linkages, enabling pre-treatment times to be reduced from several weeks to as little as one to two days while improving gelatin yield.

3.1.2. Extraction: Thermal hydrolysis in warm water (typically 50 °C to 75 °C) is employed to partially break down collagen into soluble gelatin. Erge and Zorba (2018) optimized hot-water extraction from chicken mechanically deboned meat residue and identified 76–82 °C as the most influential factor for gelatin yield, confirming that controlled thermal hydrolysis within this temperature window efficiently disrupts hydrogen and covalent bonds without excessive peptide-chain degradation. Widyasari and Rawdkuen (2014) similarly extracted gelatin from chicken feet in distilled water at 55 °C for 7 h, demonstrating that moderate temperatures in the 50–75 °C range are sufficient to convert poultry collagen into soluble gelatin fractions.

3.1.3. Recovery: The crude extract is clarified by filtration, concentrated (commonly under vacuum), and dried to produce solid, high-purity gelatin. Sarbon et al. (2013) filtered the chicken skin extract through a Büchner funnel, deionized it with mixed-bed resin, reduced the volume ten-fold by rotary evaporation at 45 °C, and finally freeze-dried the concentrate to obtain gelatin powder. Rasli and Sarbon (2015) subsequently compared freeze-drying and vacuum-oven drying of chicken skin gelatin, reporting that the drying method significantly influences rheological behavior, functional properties, and structural integrity of the final product.

3.2. Key Characteristics of Soluble Gelatin

3.2.1. Amino Acids: Gelatin recovered from poultry skin is notably rich in glycine, proline, and hydroxyproline, which are essential for stabilizing the triple-helix structure. Sarbon et al. (2013) identified glycine (33.70%), proline (13.42%), and hydroxyproline (12.13%) as the most dominant amino acids in chicken skin gelatin, while Aykın-Dinçer et al. (2017) similarly reported high levels of glycine (20.26%), proline (15.12%), and hydroxyproline (11.36%) in broiler skin gelatin.

3.2.2. Physical Properties: Poultry skin gelatin demonstrates high solubility in warm water, strong gelling capacity, and a melting point that often exceeds 33°C, comparing favorably to bovine gelatin. Sarbon et al. (2013) found that the melting temperature of chicken skin gelatin was significantly greater than that of commercial bovine gelatin, and Mohammadnezhad and Farmani (2022) recorded gelling and melting points of 16.5°C and 45.5°C,

respectively, for chicken skin gelatin versus 11.5°C and 40.5°C for bovine gelatin.

3.2.3. Rheology: Chicken-skin gelatin exhibits strong viscoelastic behavior and high Bloom values, indicating firm gel strength. Sarbon et al. (2013) measured a Bloom value of 355 g for chicken skin gelatin compared to 259 g for bovine gelatin, accompanied by superior storage (G') and loss (G'') moduli, and Mohammadnezhad and Farmani (2022) similarly observed a Bloom value of 291 g with enhanced viscoelastic properties relative to commercial bovine gelatin. These findings are further supported by Rasli and Sarbon (2015), who demonstrated that drying methods influence the rheological and structural properties of chicken skin gelatin, and by Xin et al. (2021), who confirmed comparable gel properties and nanostructures across chicken, porcine, and tilapia skin gelatins.

3.3. Physicochemical and Structural Characterization

3.3.1. Molecular and Amino Acid Profile: Dominated by glycine (~33%), proline, and hydroxyproline, forming stable α -chains and triple-helical configurations comparable to or exceeding commercial bovine standards (Sarbon et al., 2013; Aykın-Dinçer et al., 2017).

3.3.2. Rheological and Thermal Properties: Chicken skin gelatin exhibits a high Bloom gel strength (often exceeding 350 g) and elevated melting and gelling temperatures (approx. 33.5°C), showing strong viscoelastic stability (Sarbon et al., 2013).

3.3.3. Solubility and Functional Attributes: Highly soluble in hot water with exceptional water-binding, foaming, and oil-emulsifying capacities (Sarbon et al., 2013).

3.4. Food and Pharmaceutical Applications

3.4.1. Food Industry

Gelatin recovered from poultry by-products, predominantly chicken skin and feet, exhibits the full spectrum of functional properties required in modern food manufacturing. Rather et al. (2022) emphasized that poultry gelatin serves as a texture provider, water-binding agent, foaming agent, emulsifier, and colloid stabilizer, mirroring the classical functionalities established by Karim and Bhat (2009) for mammalian gelatins. In dairy and confectionery systems, these properties manifest as creamy consistency, foam stabilization, and moisture retention in low-fat spreads, ice creams, and whipped desserts (Karim & Bhat, 2009). Sari et al. (2022) provided empirical validation by demonstrating that gelatin extracted from chicken leg skin performed equivalently to commercial mammalian gelatin as a stabilizer in ice cream, with no significant differences in quality or meltdown behavior. Beyond texturization, Gómez-Guillén et al. (2011) highlighted the capacity of poultry-derived gelatin to act as a micro-encapsulating agent for bioactive compounds and probiotic living cells, thereby extending its utility from simple physical modification to functional delivery systems in meat products and fortified foods.

3.4.2. Biodegradable Packaging

The film-forming ability of poultry skin gelatin makes it a renewable material for edible and biodegradable packaging that can replace petroleum-based plastics. Sarbon et al. (2013) pioneered the systematic characterization of chicken skin gelatin, confirming its physicochemical and film-forming equivalence to mammalian sources and establishing its candidacy as a sustainable alternative. Subsequent studies have optimized composite matrices: Alias and Sarbon (2019) incorporated potato starch into chicken skin gelatin films, reporting enhanced rheological,

physical, and mechanical properties, while Loo and Sarbon (2019) developed tapioca starch–gelatin blends with improved structural integrity and barrier performance. Ramos et al. (2016) reviewed the broader field of gelatin-based coatings, noting their exceptional oxygen barrier properties, optical clarity, and inherent biodegradability. More recently, Roy et al. (2025) synthesized advances in active packaging, demonstrating that poultry gelatin films can be functionalized with antimicrobial nanoparticles or natural extracts to extend shelf life while eliminating plastic dependency. Said and Sarbon (2021) further advanced this paradigm by developing active biodegradable chicken skin gelatin composite films incorporated with curcumin, achieving both antioxidant functionality and complete biodegradability. Gómez-Guillén et al. (2009) contextualized these innovations within the global shift toward non-mammalian gelatin sources for renewable, active biodegradable packaging systems.

3.4.3. Pharmaceutical and Biomedical Uses

In pharmaceutical and biomedical sectors, poultry gelatin's biocompatibility, biodegradability, and freedom from mammalian transmissible spongiform encephalopathies (TSEs) render it an exceptionally safe excipient. Rather et al. (2022) summarized its established roles in rigid and soft capsule manufacturing, injectable drug-delivery microspheres, plasma expanders, and as a stabilizer in live-attenuated viral vaccines. The regulatory significance of sourcing cannot be overstated: the European Food Safety Authority (EFSA, 2024) quantified the BSE risk posed by ruminant-derived collagen and gelatin, concluding that while modern processing reduces infectivity, bovine and ovine sources require stringent geographical and tissue-origin controls. By contrast, avian species are not susceptible to BSE or related prion diseases, making poultry gelatin inherently exempt from these TSE transmission pathways (Scientific Steering Committee, 2000). This biological safety advantage is critical for parenteral and implantable applications where mammalian-source gelatin carries theoretical, albeit remote, risk (EFSA, 2024). In advanced therapeutics, Ranganathan et al. (2019) utilized gelatin composites for bone tissue engineering, exploiting their osteoconductive scaffold properties, while Mahmoudi Saber (2019) engineered gelatin nanoparticles for targeted drug and gene delivery, capitalizing on the polymer's mucoadhesive and controlled-release kinetics. Lee et al. (2021) further demonstrated the antimicrobial potential of chicken skin gelatin films incorporated with zinc oxide nanoparticles, suggesting cross-sector applicability from food packaging to medical-grade barrier materials. Collectively, these attributes establish poultry-derived gelatin as a strategically important biomaterial in capsule formulations, micro-encapsulation platforms, and matrix-based drug delivery systems where safety, functionality, and religious or dietary acceptability converge.

CONCLUSION AND RECOMMENDATION

Conclusion

The valorization of poultry skin waste into soluble gelatin represents a promising paradigm shift toward sustainable bioresource utilization, addressing both environmental concerns associated with poultry processing by-products and the growing industrial demand for functional hydrocolloids. This review has systematically examined the preparation methodologies, physicochemical characterization, and multifaceted applications of poultry skin-derived gelatin, revealing several critical insights.

Preparation and Extraction: Acid and alkaline pretreatments

remain the predominant approaches for demineralizing and destabilizing the collagen matrix in poultry skin, with enzymatic hydrolysis and thermal extraction serving as the primary mechanisms for gelatin solubilization. The extraction parameters, particularly temperature, pH, time, and solid-to-solvent ratio, significantly influence the yield, molecular weight distribution, and functional properties of the resultant gelatin. Optimized extraction protocols have demonstrated that poultry skin gelatin can achieve yields and quality attributes comparable to those of conventional mammalian sources, particularly porcine and bovine gelatins.

Characterization and Functional Properties: Comprehensive characterization studies confirm that poultry skin gelatin exhibits favorable physicochemical properties, including adequate bloom strength, viscosity, and gelling/melting temperatures, though these properties are inherently modulated by the bird species, age, and extraction conditions. Spectroscopic and electrophoretic analyses verify the preservation of the triple-helical structure and α -chain composition typical of Type I collagen-derived gelatins. Notably, poultry skin gelatin demonstrates superior solubility across a broad pH range and commendable foaming and emulsifying capacities, rendering it technically viable for diverse formulations.

Applications in Food and Pharmaceuticals: In food systems, poultry skin gelatin functions effectively as a gelling agent, stabilizer, film-former, and encapsulant, with emerging applications in edible coatings and active packaging that extend shelf life and enhance food safety. In the pharmaceutical domain, its biocompatibility, biodegradability, and non-immunogenic profile position it as a suitable candidate for hard and soft capsule production, wound dressing matrices, drug delivery vehicles, and tissue engineering scaffolds. The absence of religious constraints (halal and kosher compatibility) further amplifies its global market applicability relative to mammalian counterparts.

Sustainability and Eco-friendliness: From a life-cycle perspective, converting poultry skin, a low-value waste stream, into high-value gelatin aligns with circular economy principles and significantly mitigates the environmental burden of poultry slaughterhouse waste. The reduced land-use footprint, lower greenhouse gas emissions, and diminished risk of transmissible spongiform encephalopathies compared to bovine sources reinforce the ecological and safety credentials of poultry-derived gelatin.

Despite these advancements, variability in raw material quality, standardization of extraction protocols, and limited large-scale commercial production remain challenges that temper the full realization of poultry skin gelatin's industrial potential.

Recommendations

- Based on the synthesized literature, the following recommendations are proposed to advance the field and facilitate the commercial translation of poultry skin gelatin:

For Future Research

- Standardization of Extraction Protocols:** There is an urgent need for harmonized, species-specific extraction methodologies that consistently yield gelatin with reproducible functional properties. Future studies should employ response surface methodology (RSM) and artificial neural networks to model and optimize multi-parameter extraction systems.

- Structural–Function Relationship Studies:** Deeper investigations into the correlation between molecular weight distribution, amino acid profile (particularly imino acid content), and functional properties (gelling, emulsification, film-forming) are essential. This knowledge will enable tailor-made gelatin production for specific food and pharmaceutical applications.
- Scale-Up and Process Intensification:** Research should transition from laboratory-scale batch processes to pilot and industrial-scale continuous extraction systems. Studies on the economic feasibility, energy consumption, and water footprint of scaled-up operations are critical for commercial viability.
- Modification and Functionalization:** Exploration of chemical, enzymatic, and physical modifications (e.g., cross-linking, grafting, nanocomposite formation) to enhance the mechanical strength, barrier properties, and bioactivity of poultry skin gelatin-based materials is recommended.
- Safety and Regulatory Profiling:** Comprehensive toxicological assessments, allergenicity studies, and compliance evaluations with international food (Codex Alimentarius, FDA, and EFSA) and pharmaceutical (USP and EP) standards must be conducted to secure regulatory approval and consumer confidence.
- Comparative Shelf-Life and Stability Studies:** Long-term stability investigations under varying storage conditions are necessary to establish the shelf life of poultry skin gelatin in comparison to conventional mammalian gelatins, particularly for pharmaceutical-grade applications.

For Industry and Policymakers

- Integrated Biorefinery Models:** Poultry processing industries should adopt integrated biorefinery approaches where skin waste is channeled into gelatin production as a value-added co-product, thereby enhancing economic returns and achieving zero-waste targets.
- Investment in Purification Technologies:** Industry stakeholders should invest in advanced purification technologies (membrane filtration, chromatographic separation) to remove residual lipids, pigments, and odor compounds, ensuring food-grade and pharmaceutical-grade purity standards.
- Market Diversification and Consumer Education:** Given the religious and cultural acceptability of poultry gelatin, manufacturers should target halal, kosher, and vegetarian-adjacent markets where mammalian gelatin faces restrictions. Transparent labeling and consumer education campaigns can accelerate market penetration.
- Policy Incentives for Waste Valorization:** Governments and regulatory bodies should introduce tax incentives, subsidies, and grants for poultry processing facilities that implement waste-to-value

technologies, thereby accelerating the adoption of sustainable practices.

- **Collaborative Frameworks:** Enhanced collaboration between academic institutions, poultry industry consortia, and pharmaceutical companies is essential to bridge the gap between research innovation and commercial application, ensuring that laboratory findings translate into scalable, market-ready products.

4. DECLARATIONS

- Corresponding Author's E-mail: teferitwoasgedom@yahoo.com

5. AUTHOR'S CONTRIBUTION

- All authors contributed equally to this work from its inception up to the final preparation of the manuscript.

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7. CONFLICTING INTERESTS

- The authors declare that there is no conflict of interest with respect to the authorship or publications of this manuscript.

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