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ARTICLE INFORMATION	Fill in information in each box below
Article Type	Review article
Article Title	Cultured Chinese Giant Salamander Skin and Skin Secretions as a Source of Bioactive Peptides for Food and Medicine
Running Title (within 10 words)	
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Conflicts of interest List any present or potential conflict s of interest for all authors. (This field may be published.)	The authors declare no potential conflict of interest.
Acknowledgements State funding sources (grants, funding sources, equipment, and supplies). Include name and number of grant if available. (This field may be published.)	Preparation and Industrialization of Active Peptide for Giant Salamander (SXZC-2101) (Special Research Project for National Training "City and University Coconstruction") .
Author contributions (This field may be published.)	Conceptualization: Wang J, Guo H, Mohamed HHA, Yang M, Abd El-Aty AM Data curation: Guo H, Mohamed HHA, Yang M Formal analysis: Chen D, Abd El-Aty AM Validation: Abd El-Aty AM Investigation: Chen D, Pei J Writing - original draft: Liu Y Writing - review & editing: Wang J, Liu Y, Guo H, Chen D, Mohamed HHA, Yang M, Pei J, Abd El-Aty AM
Ethics approval (IRB/IACUC) (This field may be published.)	This article does not require IRB/IACUC approval because there are no human and animal participants.

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Cultured Chinese giant salamander skin and skin secretions as a source of bioactive peptides for food and medicine

Abstract

Amphibians are enjoyable globally for their culinary value and are increasingly considered alternative protein sources. However, the skin of edible amphibians, especially giant salamanders, is often discarded without much thought. However, this underutilized resource holds significant potential for yielding valuable proteins and bioactive peptides (BPs). These peptides, such as brevinins, bombesins, dermaseptins, esculentins, magainins, temporins, tigerinins, and salamandrins, possess a wide range of biological activities, including antioxidant, antimicrobial, anticancer, and antidiabetic properties. This review provides a comprehensive analysis of the various BPs derived from giant salamander skin or secretions and their associated biological functions. Furthermore, it examines the nutritional composition of giant salamanders, their production status, and the challenges surrounding the use of their skin and secretions. This review also explores the potential applications of these BPs in the food and biomedical industries, particularly as multifunctional food additives, dietary supplements, and drug delivery agents.

Keywords: Giant salamander; Bioactive peptides; Culinary appeal; Protein source; Biomedical applications

1 Introduction

Amphibians have captivated researchers for various purposes, including consumption, art, pharmacology, calligraphy, culture, poetry, entertainment, religion, and clinical studies, serving as a valuable model for understanding broader animal biology (Wake and Koo, 2018). The Chinese giant salamander (*Andrias davidianus* s.l.) stands out as the largest extant amphibian, with individuals reaching nearly 2 meters in length. In the Middle Jurassic, these salamanders are often referred to as "living fossils." Historically, they inhabited 17 provinces and municipalities across China (Geng et al., 2019). However, rampant environmental degradation, habitat destruction, and intensive fishing activities have led to a significant decline in population density (Chen et al., 2018a). Presently, Chinese giant salamanders are predominantly found in regions such as Zhangjiajie and Xiangxi Autonomous Prefecture in Hunan, Fangxian County, and Shennongjia in Hubei, among others. However, they also exist in smaller numbers in areas such as Hefeng and Enshi in Hubei, Jing'an in Jiangxi, and Liuzhou and Yulin in Guangxi (Zhang et al., 2016b; Zhao et al., 2022). Chinese giant salamanders have been classified under Appendix I of the Convention on International Trade in Endangered Species of Wild Fauna and Flora, and the International Union for Conservation of Nature has designated them Critically Endangered. Nevertheless, despite their precarious status in the wild, commercial farms often maintain excess stocks of Chinese giant salamanders (Jiang et al., 2021a).

In addition to frogs, giant salamanders have been cultivated in captivity for human consumption, particularly because of their rarity and quality of meat, predominantly in regions such as Southeast Asia, notably China (Sills et al., 2020). In traditional Chinese medicine, Chinese giant salamanders have been revered for their tonic and strengthening properties and are often used to treat conditions such as neurasthenia and anemia. All parts of the Chinese giant salamander, including the meat, bones, liver, skin, blood, and tail fat, have significant nutritional and medicinal value. Notably, the mucus secreted by the skin glands of the Chinese giant salamander has garnered attention in modern biological research for its notable bioactivity, presenting a focal point in the study of functional biological materials (Li et al., 2023). The skin glands of the Chinese giant salamander consist of granular glands and mucus glands, both of which are multicellular in nature. The granular glands, often termed poison glands, are larger, more abundant, and capable of secreting milky white fluid when stimulated. On the other hand, the mucus glands exhibit irregularly shaped glandular bodies, producing watery and transparent secretions, with both types dispersing mucus across the body surface randomly (Fu et al., 2024b; Mauricio et al., 2021).

In the production and distribution chain, waste or byproducts often emerge, spanning from manufacturing to consumption. Skin is a common byproduct that is a valuable source of collagen (Chen et al., 2021). Giant salamander waste, particularly skin waste, serves as an alternative reservoir of collagen or bioactive peptides (BPs), offering favorable physicochemical attributes and diverse bioactivities, such as antioxidant, antimicrobial, anti-inflammatory, anticancer, antidiabetic, and drug delivery properties (Indriani et al., 2023). Giant salamanders, which are sensitive to temperature and humidity, possess a unique ability to adapt swiftly to varying environments. This physiological adaptability can influence the histological composition of their skin matrices, distinguishing them from other animal skins (Yang et al., 2017). Notably, giant salamanders possess an inherent self-defense mechanism, whereby their skin secretes bioactive compounds, including antimicrobial and antioxidative agents, or even toxins, in response to challenging or perilous conditions (Wu et al., 2024).

The cultivation of giant salamanders is highly important for both the sustainable growth of the food industry and the preservation of wild giant salamander populations (Zhang et al., 2019). Currently, farmed giant salamanders are primarily distributed as niche meat products within the food market. However, in recent years, the excessive expansion of salamander farming has led to a disproportionately singular policy and industrial structure, resulting in considerable economic setbacks for salamander farmers. Many farmed giant salamanders are released into the wild without undergoing genetic or health assessments beforehand, a practice that poses significant risks. Mass releases of farmed specimens could hasten the extinction of certain species through genetic homogenization. Additionally, instability within the Chinese giant salamander farming industry often prompts the consumption of wild salamanders during periods of economic downturn. Research progress rooted in wild giant salamanders has been sluggish because of their rarity and value. To address these challenges, researchers have aimed to increase their understanding of the ecological behaviors of giant salamanders through comprehensive investigations of farmed specimens. Such studies are envisioned to provide valuable insights that can effectively inform strategies for conserving wild giant salamander resources (Luo et al., 2018).

While giant salamanders have been extensively utilized and studied, several significant issues surrounding their consumption and derivative products cannot be overlooked, encompassing ethical, health, and religious considerations. The exploitation of giant salamanders must adhere to the guidelines outlined by the International Union for Conservation of Nature (IUCN) Red List of Threatened Species. Moreover, giant salamander meat is deemed nonhalal (haram) for Muslims because of Islamic dietary laws, known as hadith. These ethical, health, and religious constraints must be carefully considered prior to human consumption to ensure adherence to regulations and prevent overexploitation. Consequently, this review delves into the current production status and nutritional composition of giant salamanders. A detailed examination of the use of amphibian skin and skin secretions for the extraction of BPs is provided, highlighting various BPs known for their diverse biological activities. Additionally, this review addresses the multiple constraints associated with the utilization and consumption of giant salamanders while also outlining potential food and biomedical applications.

2. Chinese giant salamander production and nutritional composition

2.1. Production status

Despite being widely recognized as edible amphibians, data on the global trade value of Chinese giant salamanders are limited. A comprehensive investigation combining market surveys and interviews was conducted to explore and address the domestic trade of salamanders. Reports indicate that the overexploitation of Chinese giant salamanders for food consumption has led to habitat destruction, particularly in China, where it has been listed as a Critically Endangered species by the IUCN Red List of Threatened Species (Rosa et al., 2023). Consequently, conservation efforts have been launched through collaborations between local governments and farmers to meet market demands while mitigating overexploitation. An example of such collaboration occurred in the Qinling region of China, where the government provided subsidies to initiate salamander farms, which also attracted investments from local stakeholders. Chinese giant salamander meat is typically exported as frozen deskinned meat, with other body parts, such as the head, trunk, and skin, discarded without further use. Hence, implementing diverse coordinated strategies is crucial for sustainably managing and preserving Chinese giant salamander populations while ensuring animal welfare standards and minimizing overexploitation levels.

2.2 Nutritional values

Salamanders, particularly Chinese giant salamanders (CGSs), are more highly esteemed in China than in other regions. CGS meat offers a delicate texture akin to that of fish, rendering it a favored choice for consumers. Its nutritional value and palatability are comparable to those of other terrestrial animals. Table 1 illustrates the nutritional breakdown of Chinese giant salamanders, as documented in previous studies. The variability in their nutritional profiles is influenced by factors such as biodiversity, age, sex, diet, farming methods, breeding practices, and anatomical region (Hu et al., 2019). CGS meat typically comprises moisture (ranging from 79.0% to 82.3%), protein (14.0% to 16.4%), fat (2.5% to 3.5%), and ash (0.7% to 1.1%), although its carbohydrate content remains unreported (Geng et al., 2019). He, Zhu, Zeng, Lin, Ji, Wang, Zhang, Lu, Zhao, Su, and Xing noted that while cultural and environmental factors may lead to variations in yield, the fundamental composition, nutritional benefits, and medicinal properties of these plants remain consistent. The nutritional profile of CGS meat aligns closely with that of chicken and fish per serving.

3 Composition of mucous secreted by the skin of giant salamanders

The skin of amphibians serves various essential physiological functions, such as respiration, water regulation, temperature control, excretion, reproduction, microbial resistance, and defense against predators (Walke et al., 2017). The active components found in amphibian skin secretions, which include biogenic amines, toad ligands, alkaloids, peptides, and proteins, play crucial roles in facilitating these functions (Demori et al., 2019). Specifically, the skin secretions of giant salamanders (SSADs) are composed primarily of functional proteins, peptides, and polysaccharides (Li et al., 2018).

3.1 Functional proteins

Researchers have studied the secretion of mucus, molting, and protein composition of giant salamander skin and identified 155 proteins in mucus, 97 in molting, and 249 in the skin. Notably, mucus contains 105 unique proteins, second only to the skin, whereas molting has the fewest unique proteins (Pan et al., 2020). Gene Ontology analysis revealed that some proteins play roles in various physiological processes, such as the extracellular matrix, cytoskeleton, cell junctions, cell adhesion, wound healing, immune response, and inflammation (Wang et al., 2023b). Tables 1 and 2 provide further details, and Table 3 compares proteins found in meat, eggs, and milk with those from the giant salamander, highlighting differences between them and common protein sources. However, the proteins isolated and purified from salamander skin mucus remain limited and mainly consist of glycoproteins and lectins. Glycoproteins are compounds formed by the covalent binding of short, branched oligosaccharides and peptide chains (Fairbanks, 2019). They serve as crucial components of cell membranes, plasma, hormones, and the intercellular matrix, contributing significantly to various life processes, inflammatory reactions, abnormal proliferation of cancer cells, and the immune system (Nalehua and Zaia, 2022). The secretion of mucus from giant salamander skin involves multiple processing steps, including hot water extraction, filtration, concentration, the Sevage method to remove free protein, alcohol precipitation, dissolution, dialysis, vacuum freeze-drying, separation, and purification, to obtain a pure glycoprotein matrix. One identified glycoprotein with a molecular weight of 58 kDa is γ-carboxyglutamic acid protein III (MGP III) (Jin et al., 2019).

Lectin, a nonimmune-derived glycoprotein or protein, facilitates cell aggregation and glycoconjugate precipitation and is associated with cell growth, differentiation, development, and immunity (Hendrickson and Zherdev, 2018). Wang et al. successfully extracted a 17 kDa lectin from the mucus produced by giant salamander skin, which is rich in amino acids (Wang et al., 2019).

Glycopeptides refer to compounds formed by linking short sugar chains and short peptides. When glycoproteins are hydrolyzed by proteases, they breakdown into various peptide segments with sugar chains, known as glycopeptides, which are often utilized for analyzing their sugar chain structures (Doelman and van Kasteren, 2022). Wang et al. employed marine acidic proteases to break down the mucus secreted by giant salamander skin, yielding oligosaccharide peptides with molecular weights less than 3.5 kDa (Wang et al., 2023a). Additionally, Li Wei et al. utilized the skin mucus secretion of giant salamanders as the raw material and subjected it to composite enzyme hydrolysis to obtain oligopeptides with molecular weights less than 4 kDa.

Antimicrobial peptides are small peptide compounds that are widely found in natural organisms and are important components of the body's innate immune system (Zhang and Gallo, 2016). Zhu et al. used a 5% acetic acid extraction method followed by Sephadex G50/25 gel chromatography to isolate an antimicrobial peptide with a molecular weight of 4.3 kDa from the skin mucus of giant salamanders (Zhu et al., 2018). Similarly, Yuan Rui used 5% acetic acid extraction coupled with Sephadex G200 gel chromatography to obtain antibacterial peptides with a molecular weight of approximately 10 kDa.

Table 1. Mucus, Molting, protein types and functions of the giant salamander skin

GO Biological Processes	Mucus	Molting	Skin
	Collagen alpha-1(XI) chain	Alpha1 type II collagen	Alpha1 type II collagen

Extracellular matrix organization	Collagen alpha-2(IX) chain	Collagen alpha-1(VI) chain	Annexin A2
	Collagen type I alpha 2	Collagen alpha-1(XXI) chain	Collagen alpha-1(IV) chain
	Collagenase 3	Collagen alpha-1(XXV) chain	Collagen alpha-1(IX) chain (fragment）
	Procollagen galactosyltransferase 1-A	Collagen alpha-2(IX) chain	Collagen alpha-2(IX) chain
	Procollagen galactosyltransferase 1-B	Collagenase	Collagenase 3
	Procollagen-lysine,2-oxoglutarate	Laminin-like protein epi-1	Fibronectin type III domain-containing protein 8
	Protein disulfide-isomerase	Protein disulfide-isomerase	Laminin subunit alpha-2
	-	-	Procollagen galactosyltransferase 1
	-	-	Procollagen galactosyltransferase 1-A
	-	-	Procollagen galactosyltransferase 1-B
Cell adhesion-related proteins	Annexin-B11	Alpha1 type II collagen	Alpha1 type II collagen
	Apolipoprotein A-IV	ATP synthase subunit beta, mitochondrial	Annexin-B11
	Collagen alpha-1(XI) chain	Collagen alpha-1(VI) chain	Apolipoprotein A-IV
	Galectin-2	Collagenase	B-cell lymphoma 6 protein homolog

	Galectin-7	Laminin-like protein epi-1	cGMP-dependent protein kinase 1
	LOC100135172 protein	Microtubule-actin crosslinking factor 1	Galectin-2
	Talin-2	Peripherin	Homeobox protein Hox-A7 (fragment）
	-	-	Interferon gamma
	-	-	Laminin subunit alpha-2
	-	-	Peripherin
	-	-	Plasminogen activator inhibitor 1
	-	-	Rho-related GTP-binding protein Rho6
	-	-	Talin-2
cell junction organization-related proteins	Beta-actin	Microtubule-actin crosslinking factor 1 (fragment)	Beta-actin
	Talin-2	-	Caspase-1
	Xin actin-binding repeat-containing protein 2	-	Keratin 5 (fragment)
		-	Talin-2
		-	Xin actin-binding repeat-containing protein 2
Inflammatory response-related proteins	cGMP-dependent 3',5'-cyclic phosphodiesterase	Recombination activating protein 1	Annexin A1
	Galectin-2	-	ATP-binding cassette subfamily F member 1
	Proteasome subunit beta type-4	-	B-cell lymphoma 6 protein homolog

	Recombination activating protein 1	-	cGMP-dependent 3',5'-cyclic phosphodiesterase
	-	-	Corticotropin-releasing factor-binding protein
	-	-	Galectin-2
	-	-	Indoleamine 2,3-dioxygenase 1
	-	-	Plasminogen activator inhibitor 1
	-	-	Recombination activating protein 1
	-	-	Serum amyloid P-component
	-	-	Toll-like receptor 7
Immune response-related proteins	Apolipoprotein A-IV	Chitinase domain-containing protein 1	Apolipoprotein A-IV
	DNA ligase 4	Dual specificity mitogen-activated protein kinase kinase 2	B-cell lymphoma 6 protein homolog
	Galectin-2	Ig kappa chain V-III region WOL	Caspase-1
	Ig kappa chain V-III region WOL	Peroxiredoxin-1	Cellular tumor antigen p53
	MHC class I heavy chain	Recombination activating protein 1	Collagen type IV alpha-3-binding protein
	MHC class I heavy chain maturation peptide H-2K(D)	-	Complement C1q subcomponent subunit B

	Proteasome subunit beta type-4	-	C-type lectin domain family 2 member
	Recombination activating protein 1	-	Cyclin-dependent kinase 1-B
	Uncharacterized protein (fragment)	-	DNA repair protein ERCC1
	-	-	DNA repair protein RAD50
Wound healing-related proteins	Beta-actin	78 kDa glucose-regulated protein	78 kDa glucose-regulated protein
	cGMP-dependent 3′,5′-cyclic phosphodiesterase	Annexin A5	protein Wnt-5b
	Collagen type I alpha 2	Cofilin-1-A	Annexin A2
	Heat shock cognate 71 kDa protein	Collagenase	Annexin A5
	Osteonectin	Microtubule-actin crosslinking factor 1 (fragment)	Apolipoprotein A-V
	Plasma glutamate carboxypeptidase	Peripherin	Beta-actin
	Profilin	Profilin	Cellular tumor antigen p53
	Protein Hook homolog 1	-	cGMP-dependent 3′,5′-cyclic
	Uncharacterized protein	-	cGMP-dependent protein kinase 1
	Uncharacterized protein (fragment)	-	Keratin 5 (fragment)
	60S ribosomal protein L3	Cofilin-1-A	60S ribosomal protein L19

Cytoskeleton organization-related proteins	Actin-related protein 2	Double-strand-break repair protein rad21 homolog	Actin, alpha skeletal muscle 2
	Beta-actin	Dystrophin-1	B-cell lymphoma 6 protein homolog
	Dystrophin-1	Keratin, type I cytoskeletal 9	Beta-actin
	Keratin, type I cytoskeletal 16	Peripherin	cGMP-dependent protein kinase 1
	Keratin, type I cytoskeletal 9	Profilin	Cyclin-dependent kinase 1-B
	MHC class I heavy chain	Profilin-3	Cytokeratin 8 (fragment)
	Profilin	Ubiquitin thioesterase ZRANB1	Destrin
	Protein Hook homolog 1	-	DNA repair protein RAD50
	SLAIN motif-containing protein-like	-	Double-strand-break repair protein rad21 homolog
	Talin-2	-	Glyceraldehyde-3-phosphate dehydrogenase
	Uncharacterized protein (fragment)	-	Keratin, type I cytoskeletal 19
	Unconventional myosin-Ia	-	Nucleoprotein TPR
	Xin actin-binding repeat-containing protein 2	-	Peripherin
	-	-	Protein SFI1 homolog

Table 2. Proteins (kDa) associated with physiological activities in the mucus secreted from the skin of the giant salamander.

Protein name	Molecular mass	Function
Collagen α1 (XI) chain	181.5	Bone development and collagen fiber assembly
Collagen α2 (XI) chain	65.5	-
Type I collagen α2	128.1	-
Collagenase 3	54.0	Maintenance of normal mechanical function of articular cartilage
Procollagen galactosyltransferase 1-A	71.6	Partial transfer of galactose to hydroxylysine residues of collagen- and mannose-binding lectins
Procollagen galactosyltransferase 1-B	71.8	
Precollagen lysine, 2-oxoglutarate	85.6	Collagen maturation and extracellular matrix remodeling
Protein disulfide isomerase	56.0	Catalyzes the formation, breaking and rearrangement of disulfide bonds and promotes protein folding, and is instrumental in stabilizing the three-dimensional structure of proteins
Membrane linker protein-B11	36.6	Reversible binding to phospholipid membranes, binding to calcium ions
Apolipoprotein A-IV	44.4	(i) Activates lecithin-cholesterol acyltransferase; (ii) Assists apoC-II in activating lipoprotein lipase; (iii) Liposomes of apoA-IV promote intracellular cholesterol efflux; (iv) Binds to cellular
Galactose lectin-2	15.0	-
Galactose lectin-3	15.2	Activates macrophages and microglia to induce pro-inflammatory responses
LOC100135172 protein	43.1	-

Naked protein-2	273.8	Cytoskeletal proteins that regulate cell adhesion
β-actin	42.0	Cytoskeletal proteins
Neoactin binding repeat-containing protein 2	383.9	-
60S ribosomal protein L3	22.4	-
Actin-related protein 2	44.2	Protein complexes that promote actin filament polymerization
Myotonic dystrophy protein 1	419.3	Protects cells from mechanical stress and provides scaffolding for a variety of proteins to regulate multiple intracellular signaling pathways
Keratin, type I cytoskeleton 16	51.6	Maintains cell function and skin barrier
Keratin, type I cytoskeleton 9	62.3	Keratin filament assembly
Major tissue complex class I heavy chain	15.8	-
Inhibitory protein	15.4	-
Protein hook homolog 1	83.6	Endocytosis, microscopic cytoskeleton
SLAIN motif protein	63.9	Involved in cytoplasmic microtubule organization; microtubule nucleation; and positive regulation of microtubule polymerization
Unconventional myosin	117.6	-
Unknown protein structural fragments	30.7/42.5/60.1	-
cGMP-dependent 3',5' cyclic phosphodiesterase	98.8	Cell growth and migration
Recombinant activator protein 1	53.0	-
Proteasome subunit type-IV	29.3	-
DNA ligase IV	113.3	-

Immunoglobulin K chain V-III region WOL	11.9	-
Major tissue complex class I mature heavy chain	39.6	Immunosurveillance
homologous protein	71.2	-
Osteonectin	31.2	Bone formation and remodeling
Plasma glutamate carboxypeptidase	52.1	Hydrolyzes circulating peptides in the extracellular microenvironment

Table 3. Proteins (kDa) from other sources.

Source	Protein name	Molecular mass	Reference
Egg	Ovalbumin	45	(Matsuoka and Sugano, 2022; Puglisi and Fernandez, 2022)
	Ovine transferrin	76	
	Egg-like mucin	28	
	Egg Inhibitor	49	
Milk	αs1-casein	23.615	(Fengtao et al., 2019; Kim and Lee, 2021; Maity et al., 2020)
	αs2-casein	25.226	
	β-casein	18-24	
	k-casein	19-20	
	Whey proteins	18-22	
Meat products	Collagen	200-300	(Bohrer, 2017; Lee et al., 2024; Liu and Xing, 2023)
	Myosin	51	
	Actomyosin	42-48	
	Myoglobin	17.87	
	Tropomyosin	2×35	

3.2 Polysaccharides

Polysaccharides are derived from the skin mucus of giant salamanders through various extraction methods, including alkaline, acid, water, alkaline, and acidic protease methods. The total sugar content in the extracts ranged from 1.54% to 4.23%, indicating variations based on the extraction process employed. The monosaccharide composition also varies among the mucopolysaccharides obtained through different extraction techniques. Hyaluronic acid, a polymer comprising N-acetylglucoside and D-glucuronic acid disaccharides, is predominantly found in the connective tissues of both humans and animals (Sagbas Suner et al., 2019). Although the structure of hyaluronic acid remains consistent across different sources, differences exist in its relative molecular weight. HA plays crucial roles in cell proliferation and differentiation, alleviating knee joint pain, regulating vascular wall permeability, and protecting the corneal endothelium. Yu Haihui successfully obtained hyaluronic acid through enzymatic hydrolysis and separation using diethylaminoethyl cellulose DE52, yielding 1.7041 mg/g.

4 Bioactivity of the skin-secreted mucus of the giant salamander

The components present in secretions from the skin of giant salamanders are diverse and exhibit a range of biological functions.

4.1 Antioxidant activities

The antioxidative properties of natural substances primarily involve inhibiting lipid oxidative degradation, scavenging free radicals, hindering pro-oxidants (such as chelating transition metals), and exhibiting reducing power (Vuong, 2021). *In vitro* antioxidant assessments conducted on salamander skin-secreted mucus and its derivatives demonstrated significant scavenging potential against superoxide anion radicals, DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals, and hydroxyl radicals. Moreover, this scavenging capacity was observed to increase with concentration (Fu et al., 2024a).

4.2 Antimicrobial activity

Animal mucus typically exhibits antimicrobial properties. Using the agar disk diffusion method, Wu et al. evaluated the antimicrobial activity of salamander agglutinin. These findings indicated that salamander agglutinin inhibited the growth *of Clostridium perfringens*, *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, and *Schizosaccharomyces pombe* (Wu et al., 2024). In a separate study, Yang et al. investigated the inhibitory effects of antimicrobial peptide solutions on *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus hemolyticus*, *Staphylococcus epidermidis*, and *Candida albicans* via the ring-of-inhibition method. The minimum effective inhibitory concentrations were 12 µg/mL, 16 µg/mL, 16 µg/mL, 22 µg/mL, 16 µg/mL, and 18 µg/mL (Yang et al., 2017). Furthermore, Akter assessed the impact of antimicrobial peptides on *Aeromonas hydrophila*, *Aeromonas sobria*, *Citrobacter* *freundii*, *Edwardsiella tarda*, and *Hafnia alvei*, revealing varying degrees of inhibitory effects on these bacteria (Akter et al., 2020).

4.3 Promotion of wound healing

According to historical records such as the "Collected Notes on the Classic of Materia Medica" compiled by Tao Hongjing from the North and South Dynasties, salamanders have been known for secreting skin mucus for approximately 1,600 years and are traditionally used to treat burns. Additionally, folk remedies often involve salamander skin powder mixed with tung oil for burn treatments (Zheng et al., 2021). Recent studies have confirmed the wound-healing properties of salamander skin mucus. In the experiments, lyophilized mucus powder from giant salamander skin was hydrated to form a gel. This gel exhibited excellent adhesion to adipose tissue when applied between layers of pig skin. Moreover, it demonstrated flexibility suitable for wound contact, as evidenced by a three-point bending test. In a rat skin incision model, the salamander gel effectively promoted skin wound healing and reduced scarring, as observed through histological analysis(Zhai et al., 2020). Compared with conventional surgical bioadhesives such as cellulose glue and cyanoacrylate glue, salamander skin mucus facilitates faster wound healing, boasts greater biocompatibility, and is entirely biodegradable without causing harm to the organism (Deng et al., 2019).

4.4 Antiplatelet aggregation

Chen and colleagues illustrated that salamander oligopeptides exhibit antiplatelet aggregation properties through a platelet aggregation test utilizing the whole blood resistance method. The hypothesis posits that salamander oligopeptides interact with adenosine diphosphate, consequently impeding its binding to cell surface receptors. This research holds clinical significance for treating conditions such as hypertension, thromboembolic disease, and atherosclerosis associated with increased platelet aggregation (Chen et al., 2021).

4.5 Anti-fatigue

Hepatic glycogen and creatine lactate are key indicators for assessing fatigue levels in the body (Zhou and Jiang, 2019). Increased liver glycogen stores are correlated with increased resistance to fatigue, whereas increased lactic acid accumulation indicates increased fatigue. The results revealed a 65% reduction in liver glycogen consumption in the mice in the salamander oligosaccharide peptide group compared with that in the blank control group following weightbearing swimming fatigue. Additionally, the muscle lactic acid content of the mice was 24.4% lower than that of the blank control group (Zhang et al., 2016a). These data highlight the significant improvement in the anti-fatigue capacity of mice following the administration of salamander oligosaccharide peptide.

4.6 Liver protection

Geng investigated the impact of salamander oligopeptides on liver injury induced by CCL_4. The findings revealed that the middle- and high-dose salamander oligosaccharide peptides notably suppressed the activities of serum ghrelin induced by CCl_4, reduced malondialdehyde levels, and increased hepatic superoxide dismutase activity in mouse liver tissues. Histological examination revealed that hepatocytes in the CCl_4 model group exhibited significant swelling and deformation, disorganized hepatocyte cords, and inflammatory cell infiltration. Conversely, compared with those in the model group, the salamander oligosaccharide peptide dosage groups presented an orderly arrangement of hepatocyte cords, significantly mitigating liver tissue damage (Geng et al., 2020).

4.7 Modulation of immune function

The mice were orally administered various doses of salamander oligosaccharide peptide (0.01 g/kg, 0.05 g/kg, or 0.1 g/kg) for 8 days. Serum immunoglobulin IgG levels, macrophage activity in engulfing chicken erythrocytes, and T lymphocyte function were assessed. The findings revealed notable increases in the IgG levels and macrophage counts in the mice that received salamander oligosaccharide peptide compared with those in the control group. These results suggest that giant salamander oligopeptides exert a regulatory influence on mouse immune function (Jiang et al., 2021b).

5 Safety of mucus secreted from the skin of giant salamanders

The Youyang Miscellany Chopper mentioned that people in the gorge consume salamander fish but caution against its toxicity due to the secretion of mucus from the skin of the salamander, which can induce adverse effects if ingested directly (Łaciak, 2022). Du et al. demonstrated that the intraperitoneal injection of salamander skin-secreted mucus into mice resulted in systemic and local effects, including edema and injurious sensations, at low doses(Du et al., 2016). Bletz et al. reported that the LD_{50} of skin-secreted mucus from giant salamanders was 4.64 g/kg in mice when it was administered via gavage feeding. Gas chromatography analysis identified dimethyl disulfide ($C_2H_6S_2$) as the toxic component in the mucus, although ethanol treatment rendered the mucus significantly less toxic (Bletz et al., 2018). Guo et al. conducted acute toxicity tests of salamander oligosaccharide peptides in mice via oral administration, micronucleus assays of mouse bone marrow cells, and a 30-day feeding experiment in rats. The experimental findings indicated that salamander oligosaccharide peptide levels fall within the nontoxic range (Guo et al., 2023). In conclusion, ethanol treatment or enzymatic digestion can effectively reduce the toxicity of salamander skin-secreted mucus, suggesting promising prospects for its future development.

6 Prospective Industrial Applications

6.1. Application in the Food Industry

Amphibian skin is an agricultural byproduct that is rich in proteins and lipids and serves as a valuable source for collagen, gelatin, and their hydrolysates. Gelatin and its hydrolysates have been widely used in food products as functional additives or supplements (Yokoyama et al., 2018). BPs derived from these sources have been developed and integrated into food preservatives, edible films, and coatings. Additionally, the incorporation of collagen hydrolysate (CH) into biodegradable films adds further value to the CH in the food supply chain, aligning with sustainability goals (Terauchi et al., 2023). Protein hydrolysates containing BPs contribute to biopolymer films, improving the mechanical properties and extending the shelf-life of packaged foods (Wong and Chai, 2023). BPs present in protein hydrolysates serve as functional ingredients in the food and medicine industries (Wang et al., 2022). For example, gelatin extracted from Asian bullfrog skin has a gel strength comparable to that of bovine gelatin, with studies confirming its safety for human consumption (Karnjanapratum et al., 2017). Gelatin derived from the skin of CGSs enhances foam expansion and stability, making it suitable for novel applications in food emulsion systems (Terauchi et al., 2023). CHs demonstrate bioactivities such as antioxidant and antimicrobial effects, making them suitable as daily food supplements for collagen production or regeneration in the human body. Understanding the bioaccessibility of BPs during digestion is crucial, as peptide modifications occur, generating smaller peptides with various bioactivities (Wang et al., 2023a). Proline-containing peptides, such as CH, are presumed to have high resistance to hydrolysis by digestive enzymes.

In wine production, marine microbial acidic proteases are utilized to generate low-molecular-weight glycopeptides from SSAD. These glycopeptides were incorporated into Cabernet Sauvignon grapes, which were cofermented and aged with brewing yeast to yield giant salamander wine enriched with low-molecular-weight glycopeptides (Zheng et al., 2021). The inclusion of Chinese giant salamander oligosaccharide peptides not only enhances sugar utilization efficiency during yeast fermentation but also enriches wine with 30 aroma components. Furthermore, the Chinese giant salamander oligosaccharide peptide wine exhibited potent scavenging abilities against hydroxyl and superoxide anion radicals.

6.2. Applications in the biomedical industry

In the biomedical sector, amphibian skin and secretions hold immense potential for various applications. For example, collagen derived from frog skin and CGSs represents an alternative source for tissue engineering agents (Ong et al., 2021). Collagen exhibits accelerated wound healing capabilities and enhances immunomodulation, demonstrating its function as a biomaterial scaffold. Studies involving alternative wound dressings employing collagen, particularly from marine sources, have demonstrated significant advancements in rapid wound healing in rat models (Wang et al., 2023b). Owing to their diverse bioactivities, the widespread use of collagens extends beyond the food industry to encompass the pharmaceutical sector. The use of collagen from industrial byproducts as an alternative source holds promise for preparing wound dressings (El Masry et al., 2019). Additionally, the BPs found in various frog skins exhibit antimicrobial, anticancer, antidiabetic, and immunomodulatory properties (Cancelarich et al., 2020). This underscores their potential as multifunctional supplements for specific consumer groups, such as elderly individuals or those with chronic diseases. Moreover, future cellular studies utilizing BPs in topical formulations for antiaging pharmaceuticals or as neuroprotectors hold promise for developing therapeutic strategies targeting oxidative stress in neurological disorders (Xia et al., 2021). Evaluations of the anticancer activity of BPs have further expanded their potential as future agents for cancer treatment (Wang et al., 2017). Collaborative formulations of BPs from amphibians with other bioactive compounds could pave the way for the development of novel drugs or serve as effective drug delivery agents.

6.3 Make-up development

Scientists have developed a production method for skincare products containing SSAD glycoprotein, determined the fundamental formula for these products, and performed stability assessments on the finalized SSAD glycoprotein skincare items (Chen et al., 2018b). These products adhere to quality standards and exhibit notable moisturizing properties. SSAD has antioxidant and antiphotoaging properties, and skincare formulations incorporating SSAD as a primary ingredient have demonstrated notable effectiveness in combating skin aging.

6.4 Capacitive materials

In capacitive material development, SSAD serves as a biological carbon substrate, which is uniformly mixed with cellulose nanocrystals and cellulose nanofibrils. Through unidirectional lyophilization and high-temperature carbonization, researchers have developed honeycomb-structured nanofiber carbon aerogels (Zhang et al., 2016a). Compared with alternative carbon aerogels, those incorporating SSAD-derived materials exhibit remarkable resilience in repeated compression and release evaluations. The carbon aerogel composite exhibited symmetrical properties. In addition, improvements in the electrochemical capacitance performance and cycling stability of the adhesive-free supercapacitor were observed. After 500 cycles of compression and release, the supercapacitor retained a high capacitance, indicating its robustness and electrochemical consistency.

Perspective

The Chinese giant salamander (*Andrias davidianus* s.l.) represents the largest extant amphibian population, reaching lengths of nearly 2 meters. Tracing back to the Middle Jurassic era, they are considered "living fossils." Despite being critically endangered in the wild, Chinese giant salamanders are abundantly bred on commercial farms. Striking a balance between conservation and utilization is pivotal for their future. The development of bioactive products from these salamanders can bolster the industrial cultivation of the species, thereby contributing to conservation efforts.

Currently, the use of mucus secreted from the skin of giant salamanders remains limited, largely due to insufficient exploration of its physiological mechanisms and functional components. Moreover, the high viscosity of the mucus and the use of traditional extraction methods often lead to low yields of active ingredients. Hence, there is an urgent need to adopt modern extraction and separation techniques to increase the extraction efficiency of individual components and comprehensively analyze the constituents of skin secretions.
Furthermore, by employing genomics, proteomics, and other omics approaches, this study aimed to elucidate the mechanisms underlying the secretion of skin mucus from giant salamanders via cell models, animal models, and clinical studies. These investigations offer theoretical support for the extensive exploration of salamander skin secretions. As a renewable resource with a rich

history of medicinal application, SSAD holds promise for the widespread development and promotion of functional skincare products, medical materials, healthy foods, and health supplements in the future.

Author contributions

Jinghua Wang and Yuchen Liu: Resources, Writing-Review & Editing. Hongfei Guo, Hassan Dris Abdu Mohamed and Meng Yang: Conceptualization, Visualization, Data acquisition. Dejing Chen: supervision, resources, investigation, formal analysis. Jinjin Pei: acquisition, funding acquisition, resources, investigation, review & editing. A.M. Abd El-Aty: Conceptualization, formal analysis, validation, writing -Review & editing.

Funding

Preparation and Industrialization of Active Peptide for Giant Salamander (SXZC-2101) (Special Research Project for National Training "City and University Coconstruction") .

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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