Fishery Technology 62 (2025) : 82 - 89

Jelly fish, *Acromitus flagellates* as a Potential Source of Hyaluronic Acid for Cosmetic Applications

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Abstract

Hyaluronic acid (HA) is a valuable bioactive polysaccharide that has numerous applications in the nutricosmetic and cosmetic industries. The tremendous increase of jelly fish in fishing environments has led to a huge global demand for better ways to utilize the organism. The present study investigated the potential for extracting hyaluronic acid from the jelly fish, *Acromitus flagellates.* The extracted powder was fine, hygroscopic and off-white in colour. The viscosity was measured at different concentrations of 1 mg/ml to 5 mg/ml and at the highest shear rate studied (450 s^{-1}), the maximum viscosity obtained was 1.85cp. Fourier Transform Infrared Spectroscopy (FTIR) confirmed the structure of hyaluronic acid with the presence of disaccharide repeats of D-glucuronic acid (GlcUA) and N-acetylglucosamine (GlcNAc) adjoined alternatively by â-1,3 and â-1,4 glycosidic bonds. The UV-Visible spectroscopic absorption data of the extracted sample showed similar characteristics when compared to the standard. Protein contamination was not observed in the SDS PAGE analysis. The moisture retention ability of the extracted hyaluronic acid, as estimated by in vitro analysis, was better than glycerol up to 4h. Hence, *Acromitus flagellates* is an ideal candidate for extraction of hyaluronic acid that can be applied in cosmetic and pharmaceutical formulations.

Keywords: Hyaluronic acid, *Acromitus flagellates*, cosmetic application, moisture retention, viscosity

Received 31 July 2024; Revised 16 January 2025; Accepted 29 January 2025

Handling Editor: Dr. Remya S.

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Introduction

The word hyaluronic acid (HA) was derived from the Greek word "hyalos", which means glass hence explaining the semblance of hyaluronic acid as glassy and transparent. It is a non-sulphated glycosaminoglycan (GAG) compound present in the extracellular matrix (Lepidi et al., 2006). Hyaluronic acid exhibits biodegradable, biocompatible, non-immunogenic, and receptor-binding properties. There are several biomedical applications of HA including tissue engineering, arthritis treatment, ocular surgery, drug delivery, and molecular imaging (Oh et al., 2010; Jiang, Liang J, & Noble, 2011; Zhu, Crewe, & Scherer, 2016). Up to 2 % pure hyaluronic acid and sodium and potassium salts of hyaluronic acid can be added as skin conditioning agents in cosmetics (Becker et al., 2009). The utilisation of HA in wide range of cosmetic products is associated with its strong water retention potential. It is extensively used for the treatment of wrinkles and nasolabial folds. Other roles of HA include antiaging agents, skin augmenting agents, hydrating agents and stimulators of collagen production (Bukhari et al., 2018).

The marine environment has proved to be a wellspring of naturally occurring novel therapeutic compounds. Jellyfish which belongs to the class Scyphozoa under phylum Cnidaria is a marine invertebrate, with a bell-shaped body bounded by a jelly-like substance in which its internal organs are encompassed. Massive occurrence of the jellyfish varieties is now commonly noted in the coastal waters around the globe. It is posing a major threat to the aquatic food chain and fishing. Several reports recommend its application for the production of various high-value products (Raj, Sreelekshmi, Greeshma, & Ninan, 2019) and it is widely consumed in countries like China, Japan, Malaysia,

Taiwan, Singapore and Korea (Hsieh, Leong, & Rudloe, 2001). Utilizing the jellyfish population for biofuel is another area of employing jellyfish wisely. Some species of jellyfish are observed to produce toxins, which is a concern.

The United Nations Food and Agriculture Organization (FAO) is urging cosmetics and food industries to incorporate jellyfish as a resource in the development of various products. Jelly fish was reported as a "vicious circle" vigorously feeding on young fishes causing a tremendous reduction in the resilience of fish populations is an issue of sustainability, and can be overcome by the interference of the cosmetic industry by choosing this invertebrate species as a candidate for their products. Although several works on utilisation for its bioactive properties are reported (Frazão & Antunes, 2016; De Domenico, De Rinaldis, Paulmery, Piraino, & Leone, 2019; Riccio et al., 2022; De Domenico et al., 2023), there is no report on the extraction and characterisation of hyaluronic acid from *Acromitus flagellates*. Hence production of hyaluronic acid from jelly fish is a novel area which can enable the utilisation of the resource in cosmetic applications with the added benefit of environmental improvement.

Materials and Methods

The jellyfish, *Acromitus flagellates* was collected from a Chinese dip net operated in the Kumbalangi area of Ernakulam district, Kerala, India. It was directly collected from the dip net operated by fishermen in an insulated ice box and brought to the laboratory under iced conditions. Fresh jellyfish were cut into pieces, and subjected to drying at a temperature of 40! for 8h. The dried jellyfish was collected and stored inside a desiccator until further use.

The extraction method used was as per Sanmin (2013) with minor modifications. The dried sample was added to 3 parts by weight of acetic acid and subjected to reflux heating for 6h. It was then filtered and the filtrate was added to Seavg reagent, given constant stirring and allowed to stand for proper separation. The supernatant was collected and added to 2 parts by weight (v/v) of 95% ethanol, stirred and allowed to stand to get further separation. The supernatant was filtered and vacuum-dried at 60 ^{o}C for 8h. The resultant product was immediately collected and stored for further characterization.

pH of the extracted compound was analyzed by dissolving 5 g sample in 45 ml distilled water. The mixture was minced well. The resultant slurry was then subjected to analysis in the pH meter (EcoScan pH 5, EUTECH Instrument).

The viscosity (η) of HA is a major characteristic that influences its application as an active ingredient in cosmetics. Viscometer (Brookfield DV-E Viscometer) was used for the analysis. The shear rate (γ) used was 11.3 s^{-1} to 450 s^{-1}. The extracted HA was subjected to analysis at different concentrations from 1 mg/ml to 5 mg/ml. Water was used as a standard for analysis.

FT-IR spectra of the extracted sample was studied to compare the compounds with the standard to get a confirmation of the extracted sample as HA. The samples were analysed using (Nicolet iS10 FTIR Spectrometer, Thermofisher Scientific India PVT, Ltd Mumbai). The wavelength 600-4000 cm^{-1} was used for the study through transmittance mode.

The UV-Vis absorption spectrum was measured using a UV-Vis spectrophotometer (Lambda 25 UV/VIS Spectrometer, PerkinElmer, Inc.). The measurement of absorbance characteristics was done in the 190–450 nm range for both the extracted sample and standard dissolved in distilled water (Kulkarni, Patil, & Chavan, 2018). Distilled water was used as the blank.

To confirm the purity of the extracted sample, the HA sample was subjected to SDS Polyacrylamide gel electrophoresis. The SDS protocol was performed following the method of Laemmli (1970). The sample was run on 10 % gel along with the protein marker (Bio-Rad Laboratories, Inc., USA).

The drier-based moisture absorption method was carried out according to Yang et al. (2021) with minor modifications. Take 1 mL of the extracted hyaluronic acid solution (1 mg/mL) and add it to an Eppendorf (EP) tube. The Eppendorf tubes were placed in the dryer with an ambient humidity of 43%, and each tube was positioned flat to measure its quality change in 12h. Glycerol (glycerol: water = 1:3) was used as the positive control and solvent as the blank control to determine the water loss rate of the sample. The rate of water loss was calculated using the following equation,

Water loss rate = (M_1/M_2) X 100 (%)

where M_1 represents the mass (g) of the sample before placing it in the dryer

M_2 represents the mass (g) of lost water.

Results and Discussion

Utilization of jellyfish for extraction of HA is highly recommendable to the cosmetic industry because of the abundance and low cost of the raw material. The extraction of hyaluronic acid was reported from different sources like rooster comb (Kulkarni et al., 2018), vitreous humour (Schmut & Hoffmann, 1981) and human umbilical cord (Shiedlin et al., 2004). The jellyfish species used in this study was *Acromitus flagellates* which don't impart any major threats or allergens to humans (Bijukumar & Nair, 2014).

One of the most hygroscopic molecules in nature is hyaluronic acid (Bansal, Kedige, & Anand, 2010). The extracted product appeared to be highly hygroscopic and was stored without any exposure to moisture. The production of hyaluronic acid from the complexes of other polysaccharides and proteins is usually done with detergents, enzymes, organic solvents and anion exchange resin (Han et al., 2004). However, these technologies witnessed technical difficulty in the separation of proteins, and nucleic acids and therefore not recommendable for industrial scaling up (Reddy & Karunakaran, 2013). The extraction technique adopted in this study was simple, less time-consuming and cost-effective.

HA in solution exhibits a secondary structure characterized by an expanded random coil conformation of 500 nm, with chain stiffness induced by hydrogen bonds (Alkrad, Mrestani, Stroehl, Wartewig, & Neubert, 2003). Previous studies have reported that shear thinning (pseudoplastic) behaviour is exhibited by HA solutions at moderate concentrations and low shear rates (Kim, Chang, Kim, Kim, & Kho, 2018). The viscosity (η) of extracted hyaluronic acid was studied for different concentrations from 0.1mg/ml to 0.5mg/ml and the flow curves are given in Fig. 2. At higher shear rates, the η of the samples reduced irrespective of the concentration. Maleki, Neale, Arora, Henderson, and Keeney (2007) explained that increasing the shear rate leads to the breakdown of network structures, with no mechanical degradation occurring in the polymer chains. In the present study, the reduction in η of solution with an increase in shear rate has shown that the extracted powder has pseudoplastic behaviour. This decrease in η was lowest for the concentration of 5 mg/ml than the samples of lower concentrations. This may be due to the reduction in reorganisation tendency of chains at the highest concentration studied. The flow curve showed higher values of η at higher shear rates. With an increase in the concentration of HA, the η ranged from 0.84cp to 2.08cp at a shear

Table 1. Analytical properties of the extracted hyaluronic acid

Appearance	Fine powder
Nature	Hygroscopic
Appearance in solution (1%)	Clear
pH	6.5±1.0
Colour	Off-white
Solubility in water	Soluble
Solubility in organic solvent	Insoluble
TPC	<100/G
Yeast/mould	Nil

Fig. 1. Vaccum dried hyaluronic acid from jellyfish

rate of 11.3 s^{-1} and ranged from 0.42 to 1.85 cp at a higher shear rate of 450 s^{-1}. According to Kim et al. (2018), hyaluronic acid with a molecular weight of 10 kDa exhibited viscosities ranging from 0.74 to 0.88 cps, while 100 kDa HA showed values between 0.74 and 2.38 cps, and 1 MDa HA exhibited viscosities ranging from 0.97 to 28.1 cps.

FTIR is the confirmation tool for the identification of functional groups and organic compounds by understanding the transitions between the vibrational bond status present within the molecule. The major peaks (cm^{-1}) observed for the extracted hyaluronic acid were similar to the standard hyaluronic acid (fig. 4). A distinct peak at 1084.48 indicates C-O-C stretching, also another peak at 1416.07 shows the presence of C-O group with C=O combination. Another definite peak at 1639.83 was observed, which indicates the presence of amide group (Hamad, Taha, Hafez, & El Sohaimy, 2017). This peak represents the characteristic amide I band (Pan, Pereira, da Silva, Vasconcelos, & Celligoi, 2017). It was reported that the peaks at 1639 and 1416 cm^{-1} are attributed to the asymmetric (C=O) and symmetric (C-O) stretching of the planar carboxyl groups present in the hyaluronate (Pan et al., 2017; Choi, Kim, Kim, Kweon, & Lee, 2010).

A very minor peak at 2914 was observed, which depicts the presence of C-H stretching. Also, a peak at 3269.85 establishes the O-H stretching. Along with this, some other minor peaks were also observed. These five characteristic peaks obtained from the tested hyaluronic acid sample were similar in place when compared to the standard. Hence it clearly confirmed the similarity of the tested sample of hyaluronic acid with standard hyaluronic acid. The FT-IR band model validated the structure of hyaluronic acid with the presence of disaccharide repeats of D-glucuronic acid (GlcUA) and N-acetylglucosamine (GlcNAc) adjoined alternatively by $-1,3 and $-1,4 glycosidic bonds.

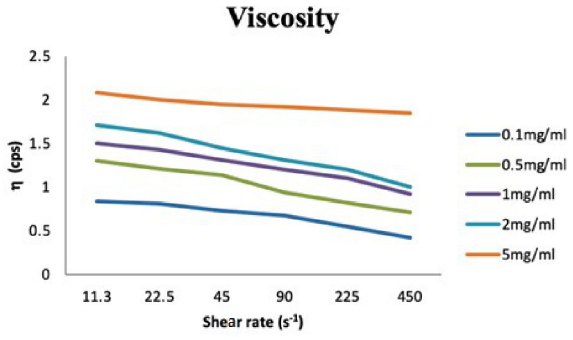

Fig. 2. Change in viscosity values of the hyaluronic acid at various concentrations

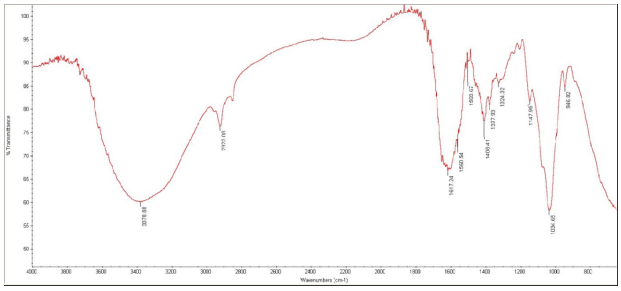

Fig. 3. FT-IR spectra of the standard hyaluronic acid

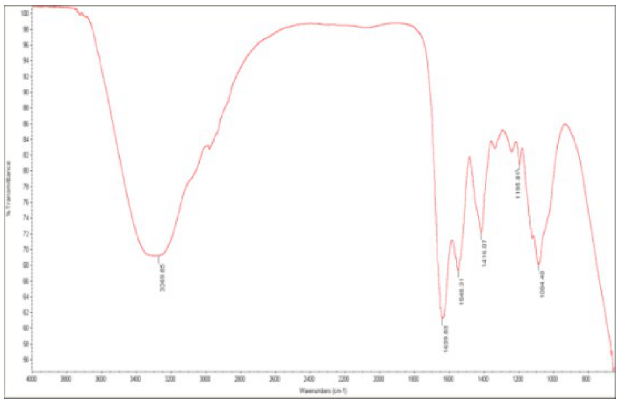

Fig. 4. FT-IR spectra of the extracted hyaluronic acid

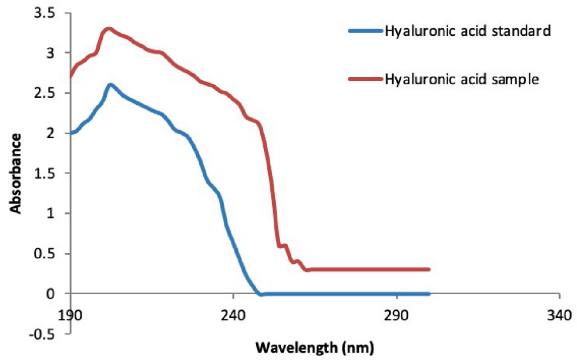

Fig. 5. UV-Vis spectra of the standard hyaluronic acid and extracted hyaluronic acid from jellyfish

The UV-Vis spectra of the HA extracted from jellyfish are shown in Fig. 5. The spectra of HA extracted in this study were compared with that of HA standard and it was seen that both had almost

similar absorbance characteristics. There was an initial increase in the absorption and then a gradual reduction in both the sample and standard. The absorbance reduces steeply after this and is followed by a constant absorption. Both spectra had absorbance maxima at 204 nm but the HA from jelly fish had a reduced absorbance of 2.56 when compared to that of the standard (3.25). It was reported that absorbance at ~210 nm was attributed to carboxyl groups (Choi et al., 2010). A maximum absorbance at 205nm was showed by Hyaluronic acid from *Streptococcus zooepidemicus* from sugar cane molasses (Pan et al., 2017) while that from rooster comb had maximum absorbance at 191.4nm (Kulkarni et al., 2018).

SDS-PAGE (Fig. 6) was performed on the extracted compound to confirm the absence of protein contamination in the sample. The extracted sample was allowed to run in 10% gel along with a marker to identify the size of protein groups, if present in the sample. The sample was run in duplicate. No protein band was obtained in the well loaded with HA from jelly fish. Hence there was no impurity in the sample extracted. SDS-PAGE was used as a confirmatory test for the purity of hyaluronic acid extracted from rooster comb, as reported by Kulkarni et al. (2018).

Moisturizing skin is a vital part of maintaining skin health. Moisture content directly influences the barrier property and controls seborrheic dermatitis. Hyaluronic acid, a Glycosaminoglycan (GAG) compound is a major factor in dermal skin matrix found in tissue and body fluid. Hyaluronic acid primarily contributes to moisture retention, tissue rejuvenation, and protection against ultraviolet rays in the skin (Laurent & Fraser, 1992; Sherman, Sleeman, Herrlich, & Ponta, 1994; Ganceviciene, Liakou, Theodoridis, Makrantonaki, & Zouboulis, 2012). As the hyaluronic acid content in the skin reduces it decelerates the process of tissue repair and moisture replenishment in the skin (Adams, Lussier, & Peyron, 2000; Cowman & Matsuoka, 2005). This compound plays a vital role in exhibiting skin dryness occurring mainly due to ageing (Fraser, Laurent, & Laurent, 1997) as hyaluronic content in the epidermis of the skin decreases as age progresses (Goberdhan, Makino, Irvine, Fleck, & Mehta, 2016). The moisture-locking ability of HA from jelly fish was studied using water as blank and glycerin as positive control (fig. 7). The study was conducted under constant temperature conditions. In the initial

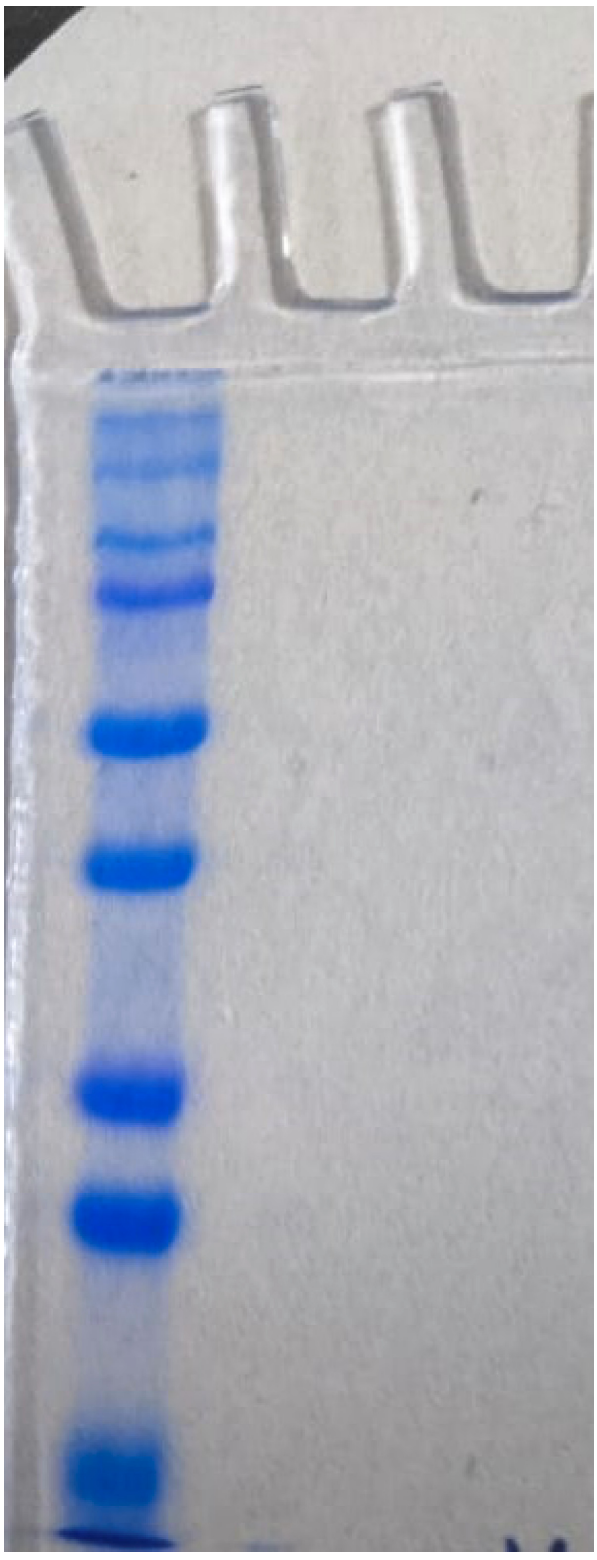

Fig. 6. SDS PAGE gel image for detecting the protein contamination

0-4 h hyaluronic acid showed better water-locking properties when compared to glycerin. At 6h, the rate of water loss from both HA and glycerin was 0.4% w. After 8 hours of treatment, hyaluronic acid exhibited a higher rate of water loss compared to glycerin. Water exhibited the highest loss rate across all time intervals, starting at 1.00% at 2 hours and gradually decreasing to 0.75% at 10 hours. Glycerol maintained a relatively stable and lower loss rate (between 0.50% and 0.35%), indicating its hygroscopic properties and resistance to evaporation. HA showed an increasing trend in water loss, starting at 0.25% and rising to 1.00% by 10 hours. This behavior suggests a delayed moisture release, possibly due to its water retention characteristics. This supports the report by Baumann (2007) who explained the high hydrophilicity of HA. This may be achieved by forming a special coiled structure (Cowman & Matsuoka, 2005) by the compound, which exhibits the nature of an ideal lubricant (Lin, Liu, Kampf, & Klein, 2020). According to Bansal et al. (2010), 1 g of HA can bind about 6 L of water and the property of formation of hydrogen bonding between adjacent N-acetyl and carboxyl groups in aqueous solutions results in conformational changes to retain water. These results ensure its utilization as an excellent moisturizing agent and emphasize its utilization in cosmetic products

This study demonstrated the feasibility of extracting high-quality hyaluronic acid (HA) from the jellyfish *Acromitus flagellates*, addressing both the increasing demand for bioactive compounds in the nutricosmetic and cosmetic industries and the environmental challenge posed by jellyfish proliferation. The rheological properties indicated a maximum viscosity of 1.85 cp at 450 s^{-1}, with UV-Visible spectroscopy data comparable to the standard, confirming its optical and structural characteristics. Importantly, the absence of protein contamination in SDS-PAGE analysis underscores the purity of the extracted HA. Furthermore, the *in vitro* moisture retention analysis demonstrated superior hydration properties compared to glycerol, maintaining efficacy for up to 4 hours. These findings highlight *Acromitus flagellates* as a promising and sustainable source of HA suitable for cosmetic and pharmaceutical formulations, offering both commercial potential and a novel approach to the valorization of jellyfish biomass.

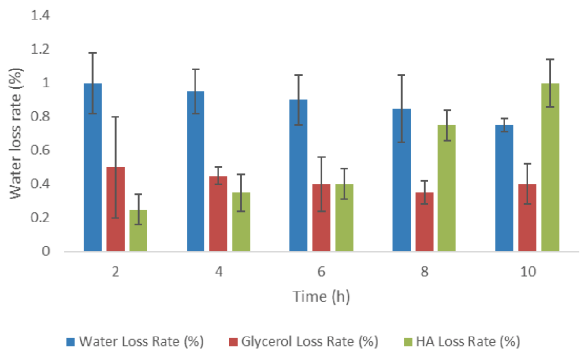

Fig. 7. Graphical Analysis of Comparative Moisture Absorption in a Dryer-Based Experiment

Acknowledgments

The authors thank Director, Indian Council of Agriculture Research-Central Institute of Fisheries Technology, Cochin India for providing facilities to undertake this work.

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