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Research Article

Effects of Various Processing Methods on the Ultrastructure of Tendon Collagen Fibrils from Qinchuan Beef Cattle Observed with Atomic Force Microscopy

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Atomic force microscopy was utilized to study the effects of ultrasound oscillation, microwave heating, water bath cooking, and acid-base soaking on the ultrastructure of collagen fibrils of Qinchuan beef cattle tendons. D-spacing length and roughness of collagen fibrils always showed a 1.02% increment in the group which was processed for 20 min rather than for 10 min under different ultrasound frequencies. Microwave heating had a slight impact on D-spacing length and roughness at lower power (140–560 W), and collagen fibrils always showed a 1.02% increment for 20 min. Then, visible changes were noted with increasing power and time. D-spacing length reduced by 1.01% at 50°C for treatment periods of 10 min, 20 min, and 30 min, and there was no obvious change at 60°C; the periodic structure disappeared after cooking for 20 min, when fibrils had become gelatinized at 70°C. Collagen fibrils became disorganized at pH 3, following acid-base soaking. The present study indicated that acid-base soaking had an outstanding effect on the ultrastructure of collagen fibrils, especially in an acidic environment in consideration of the special structure of collagen.

1. Introduction

Qinchuan beef cattle belong to large animals, that is, meat combination with strong limbs and big hoofs. As the main composition of beef tendons, collagen fibrils are the most abundant proteins in mammalian tissues, accounting for more than 30% of the total protein [1]. It is the extracellular matrix framework that is synthesized and secreted from cells of fibroblasts, chondrocytes, osteoblasts, and some epithelial cells [2]. Type I collagen is the most abundant and typical in all types, which mainly exists in skin, bones, tendons, cornea, and teeth [3–5]. The current molecular model of the D-period involves two regions, one where all the molecules overlap and one where 20% of the molecules are missing due to an axial gap [6, 7].

In the food industry, collagen has been applied to improve elasticity and stability of various products such as beverages, soups, pasta, and meat [8]. Collagen hydrolysates have played an important role in protein supplements, particularly in maintaining the inner-corporal nitrogen balance. The hardness of collagen could be applied to identify meat tenderization because different meats contain different collagen contents. Recently, it has been used as an index of meat quality. On the one hand, collagen is significant to build up the tenacity of muscles and bones, especially for those who have been suffering from lumbar debility and physically weak bodies and on the other hand, collagen ensures that adolescents grow healthy and elderly people suffer less from osteoporosis. Moreover, it can accelerate wound healing [9]. In addition, beef tendon foods can be used as additives, nutrition enhancers, etc.

Ultrasonication, microwave heating, water bath, and acid-base soaking [10–13] were performed to study the

effects on the ultrastructure of collagen fibrils of beef tendons. The aim of these studies was to induce structural changes to promote collagen processing. Such changes could also catch about the external ultrastructure and mechanical properties of collagen fibrils by atomic force microscope (AFM) [14], which is a suitable tool to acquire superficial information. AFM has been applied to take molecular- and atomic-scale measurements on biological systems. This scanning probe microscope (SPM) has allowed the study of biological systems, similar to that experienced in the fields of solid-state surfaces and interfaces [15–17]. AFM is a new instrument with high resolution at the atomic level, not only to collect topological images of cells and biomacromolecules at a nanoscale resolution, but also to detect microscopic local mechanical properties [18, 19]. Therefore, it may be an effective tool to study the collagen fibril's nanostructure and mechanical properties quantitatively for further research. The limitations of the AFM technique are linked to impurities covering a sample's surface.

In the present study, the research focus on distinct processing methods influenced the ultrastructure of collagen fibrils, but they all disrupted the ordered arrangement with higher intensity.

2. Materials and Methods

2.1. Preparation of Beef Tendon. The tendon tissues from 18-month-old Qinchuan beef cattle were offered by Prof. Zan at the National Beef Cattle Improvement Center of Northwest A&F University. These tissues were placed in centrifuge tubes and stored at −20°C in a refrigerator until further processing and analysis. The beef tendon tissues were cut into 0.3 cm^3 cubes and were homogenized intermittently in distilled water using a T10 IKA homogenizer (IKA Co., Germany) until homogeneous floccules occurred.

2.2. Ultrasonic Oscillation of Beef Tendon. The prepared 1 ml beef tendon homogenate was oscillated by using an ultrasonic bath (Ningbo, Scientz Biotechnology Co., China) at 20, 28, and 40 kHz for 10 and 20 min separately. During the processing, ice cubes were added into the bath in order to reduce the thermal influence by a potential temperature increase during the sonication process. Thus, the temperature was regulated at about 25°C.

2.3. Microwave Heating of Beef Tendon. The prepared 20 μl homogenized tendon droplets were deposited onto freshly cleaved mica and heated in a S0-microwave oven (Galanz Co., China). Microwave power was set to 140, 280, 420, 560, and 700 W for 5, 10, and 15 min. To maintain air humidity, a cup of water was made available for the microwave oven before microwave heating.

2.4. Water Bath Heating of Beef Tendon. The raw material of tendon was homogenized with 1 ml of homogenized liquid and transferred into centrifuge tubes. Then, this was placed in a HH-6 constant temperature water bath (Guohua Apparatus Co., China) at 50°C, 60°C, and 70°C for 10 min, 20 min, and 30 min, respectively. During the heating process, homogenized tendons of some treatment groups reunited and they were homogenized again to ensure uniform floccule formation.

2.5. Acid-Base Soaking of Beef Tendon. Both 0.1 M HCl and 0.1 M NaOH were used to adjust pH values to 3, 5, 7, and 10. Tendon homogenate in each treatment group was centrifuged at 1500 rpm for 2 min, and then, the supernatant was filtered. This was added to 1 ml solutions of different pH values in each centrifuge tube and incubated for 7.5, 15, and 25 h. The treated groups were centrifuged again at the same speed and 1 ml of distilled water was added into the precipitate for resuspension.

2.6. AFM Imaging and Data Analysis. The tendon samples were deposited onto freshly cleaved mica and placed in a ventilated place for air-drying and fixing, before rinsing 3 times with distilled water. Each treatment was replicated three times. All tests were carried out on a Multimode-8 AFM with SCANASYST-AIR probes (Bruker Co., Santa Barbara, CA) in ScanAsyst mode at 0.997 Hz. Height and error images in 512×512 pixels were collected simultaneously after a second order flatten, local filtering, and noisy line erasing using AFM offline software NanoScopeAnalysis V1.10 (Bruker Co., Santa Barbara, CA) to collect data on D-spacing length (DSL) and roughness of collagen fibrils. All the data were obtained from two-factor cross interactions, and the significance level was set at 0.05. All statistical analyses were performed by SAS8.0 (North Carolina, USA) using original DSL and roughness data from AFM height images of collagen fibrils associated with different processing methods and durations.

3. Results and Analysis

3.1. Effect of Ultrasonic Treatment on Collagen Fibrils. Typical AFM height images of collagen fibers with section analysis result are shown in Figures 1(a)–1(c). D-spacing length (DSL) was measured with the section profile in Figure 1(c) due to the periodic structure of collagen fiber.

AFM height images of collagen fibrils are presented in Figure 2 for different ultrasonic frequencies and treatment times. With the increase of frequency and time, the ultrastructure of the collagen fibrils became obscured, especially during treatment at 28 kHz and 40 kHz for 20 min, as shown in Figure 2. The changes of DSL were nonsignificant when the ultrasonic frequency was at 20 kHz; this would suggest that the triple-helix structure of the collagen molecule was stabilized by ultrasonic low-frequency treatment [20]. But it reached a maximum value of 71.86 ± 1.16 nm at 28 kHz sonication for 10 min. The DSL of the 20-minute group was greater than that of the 10-minute group at the same frequency. Chang et al. [21]

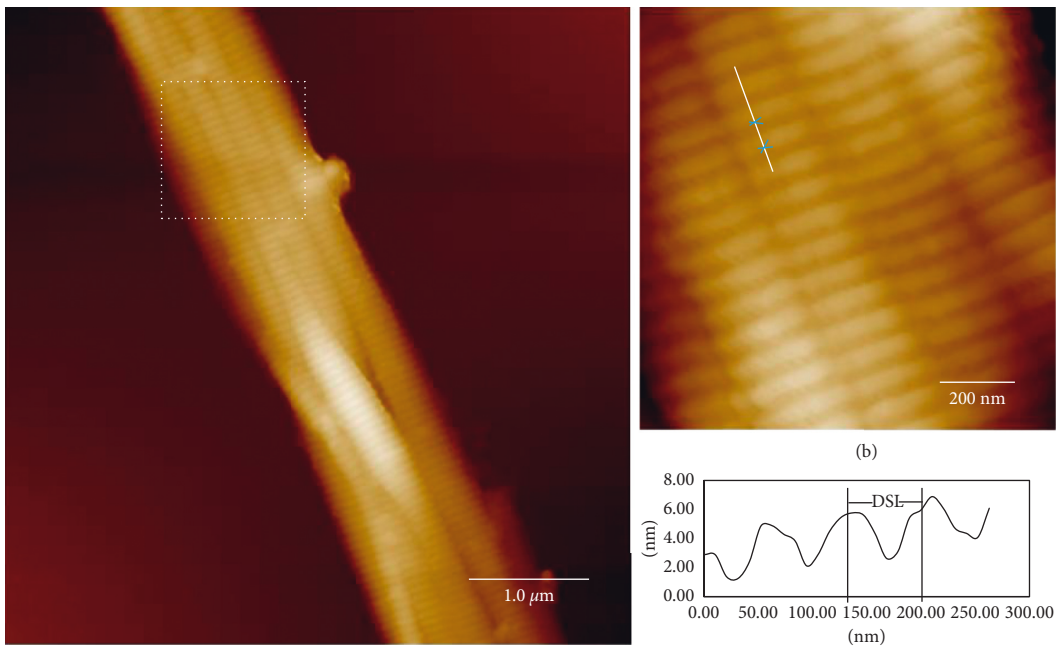

Figure 1: Typical AFM height images of collagen fibrils. (a) Control group, (b) partial amplification of white dotted line in (a), and (c) section analysis profile of collagen fibrils along the white line.

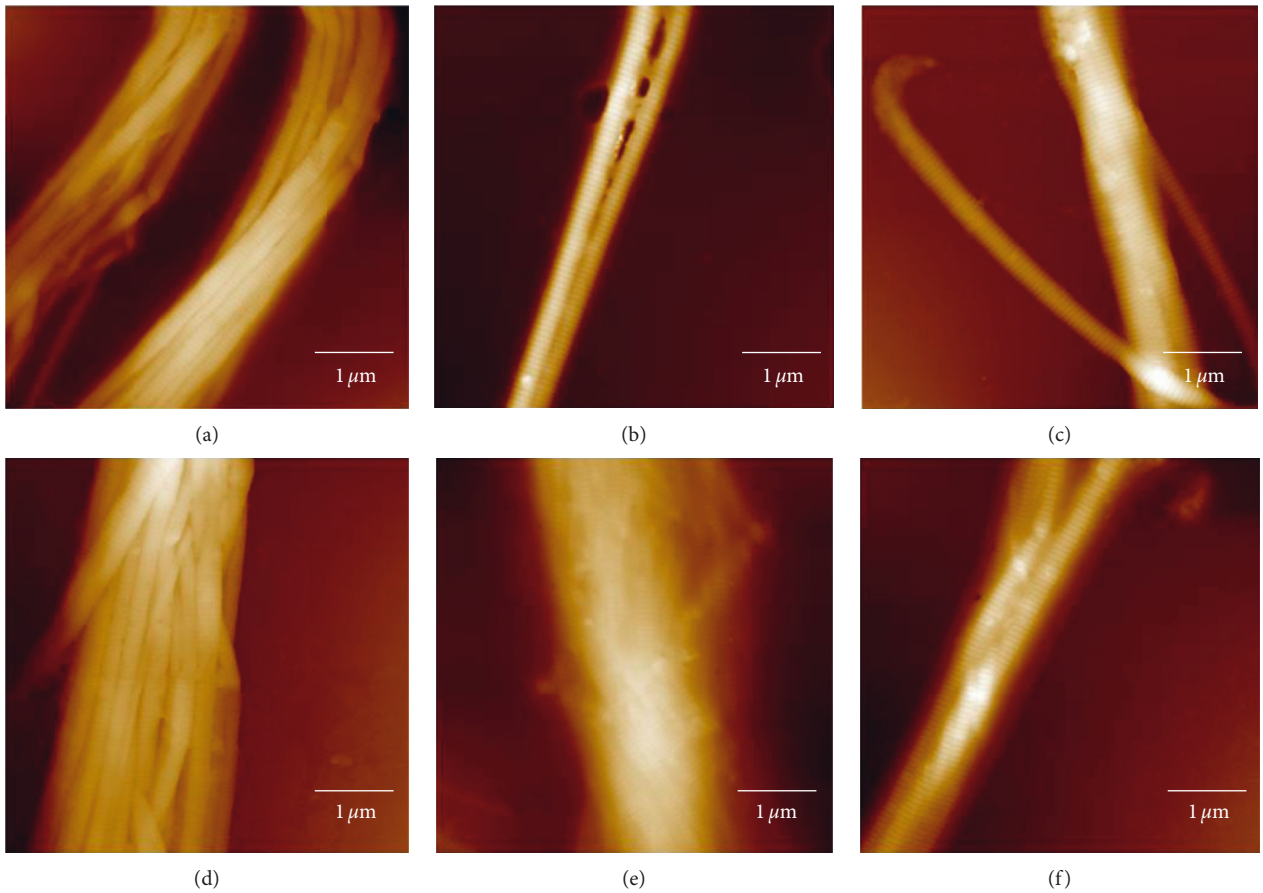

Figure 2: Typical AFM height images of collagen fibrils treated by ultrasound at different frequencies: (a–c) 10-minute group and (d–f) 20-minute group were processed at 20, 28, and 40 kHz, respectively.

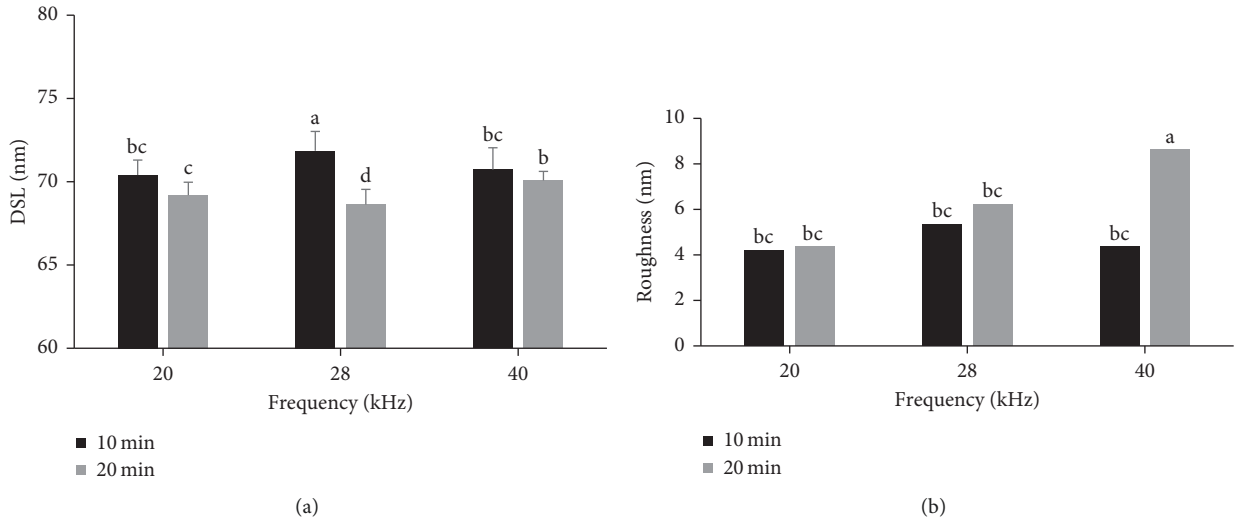

Figure 3: DSL (a) and roughness (b) of collagen fibrils under different ultrasonic frequencies and times. a, b, c, and d values in the row and column; entries with the same superscript are not significantly different ($p \geq 0.05$).

studied the effects of ultrasonic treatment on collagen fiber ultrastructure and biomechanical properties of semitendinosus quality, indicating that collagen fibers were significantly disordered and staggered, and fiber arrangement became loose and denatured; it was the same phenomenon as shown in Figure 2. For scleroprotein, like collagen fibers, there was no significant impact on its surface morphology without any side effects, just cavitations after ultrasonic processing [22].

As shown in Figure 3, there was no significant difference ($p > 0.05$) for roughness at different frequencies for 10 min, perhaps linked to the short sonication time. With a long time and high frequency, the roughness was up to the maximum (8.62 nm), which increased by 201.4% compared with the minimum value of 4.28 nm for the treatment group in 20 min. On the whole, roughness following sonication for 20 min was greater than that for 10 min at the same frequency, indicating an effect on the understructure.

3.2. Effects of Microwave Treatment on Collagen Fibrils. AFM height images of collagen fibrils are shown in Figure 4 for different microwave powers and treatment times. With increasing time and power, the periodic structure of collagen fibrils was lost by degrees and even disassembled from the fibril end. There was no significant variation in length and structure from the data and pictures among diverse power, thus, they were not listed for the 5-minute group. For the 15-minute group at 560 W and 700 W, the periodic structure disappeared, so there were no DSL data; DSL became longer for the 15-minute group than for the 5-minute and 10-minute groups. And the difference of DSL was not significant under 5 min and 10 min treatment time. The low microwave power and treatment time cannot change the DSL of collagen fibril maybe because of its stability [23]. With microwave power increasing, great changes occurred in the collagen ultrastructure, especially at 700 W for the groups of 10 min and 15 min, as shown in Figures 4(e) and 4(j). Overall, DSL was minimized at 140 W for the 15-minute group and maximized at 420 W for the 15-minute group.

The collagen fibrils were heated for 5 min in the microwave oven at different power levels as set out in Figure 5. The periodic structure disappeared when at 700 W for the 10-minute group, but the roughness varied repeatedly with the power going up. For the 15-minute group, the structure disappeared at 560 and 700 W. Overall, the roughness was minimum at 700 W for the 5-minute group and maximum at 700 W for the 15-minute group. So, we inferred that the disordered structure of microwave treatment can increase the roughness of collagen fibrils.

3.3. Effects of Water Bath Heating on Collagen Fibrils. Water bath treatment had a strong impact on collagen fibrils. Different temperatures (50°C, 60°C, and 70°C) and processing times (10 min, 20 min, and 30 min) had significant effects on the surface morphology of collagen fibrils. The periodic collagen fibril structure could be observed at 50°C and 60°C. But this partially disappeared at 70°C for the 10-minute group, with collagen fiber structure completely disappearing for the 20-minute and 30-minute groups. This suggested that granular protein had been gelatinized as shown in Figures 6(h) and 6(i) and similar changes were observed by Chang et al. [12]. And it was coincident with the research of Liu that collagen thermal denaturation is a time-dependent irreversible transformation [24].

At 50°C, DSL reduced gradually over time; at 60°C, DSL became irregular and achieved the largest value when heated for 20 min but had no obvious changes. It was judged that the triple helices of collagen began to disintegrate at 70°C for the 20-minute and 30-minute groups in the present study; Xiao et al. [25] studied the law of conformational changes of collagen under heating conditions (15°C–95°C), and as temperature increased, the native triple helical structure of

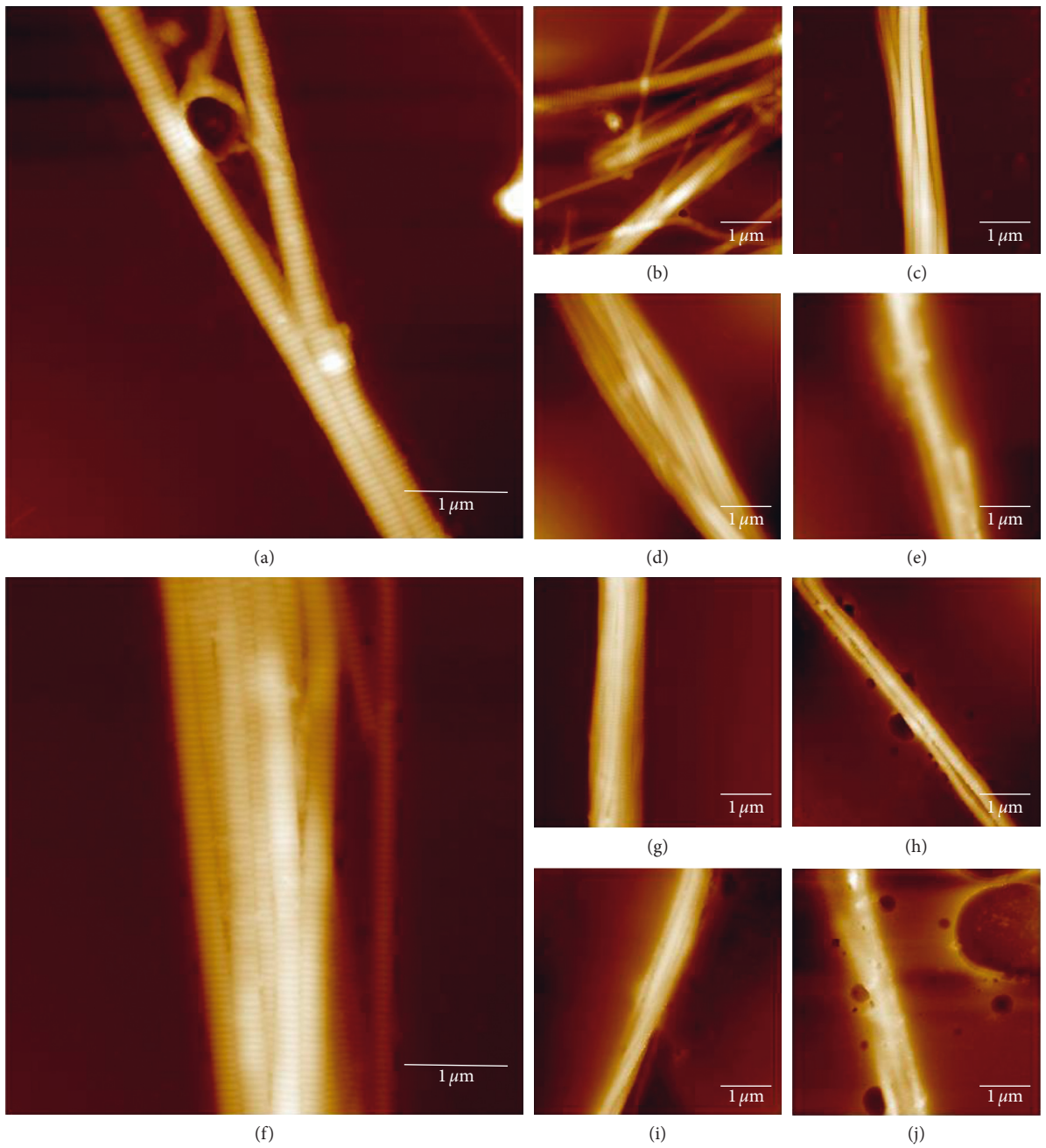

Figure 4: Typical AFM height images of collagen fibers treated by microwave. (a–e) 10-minute group and (f–j) 15-minute group were processed at 140, 280, 420, 560, and 700 W, respectively.

collagen gradually broke up and the disordered structure of protein was augmented. With a longer time or higher temperature, DSL became shorter and it was likely due to the effect of denaturation and shrinkage of collagen fibers during heating. Ma and Ledward also reported that collagen in connective tissue denatures and unfolds when the temperatures is 60–70°C [26].

DSL of collagen fibrils was influenced by water bath heating and so was roughness. With the time increasing, roughness decreased little by little as shown in Figure 7 at 50°C; over time, roughness rose gradually at 60°C; and the periodic structure disappeared at 70°C. In general, roughness at 70°C was greater than that at 50°C and 60°C for the three time periods, and it was up to the maximum for the 10-minute group at 70°C. The collagen fibril roughness increased with the disappearance of the triple helical structure as with the microwave treatment.

3.4. Effects of Acid-Base Soaking on Collagen Fibrils. The solutions with different pH values had an obvious effect on the collagen fibers' surface morphology, especially at pH 3 (Figure 8). After acid-base soaking, opaque white floccules became translucent lumps in the centrifuge tube. Chaotic arrangement and small fragments were notable from the pictures at pH 3. A wide range of periodic structures

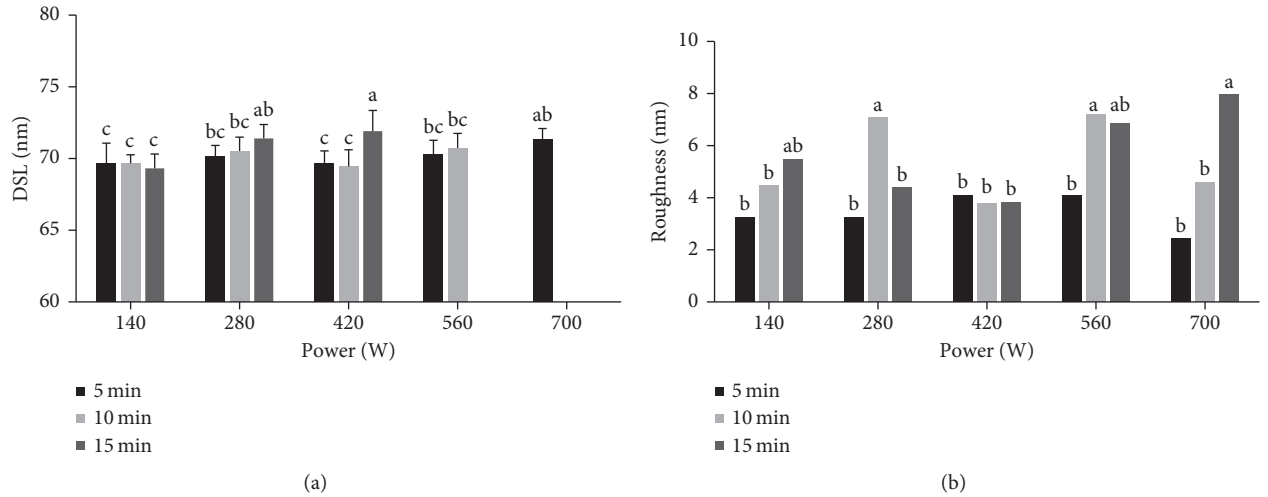

Figure 5: Changes of DSL (a) and roughness (b) of collagen fibrils under different microwave powers and times. a, b, and c values in the row and column; entries with the same superscript are not significantly different ($p \geq 0.05$).

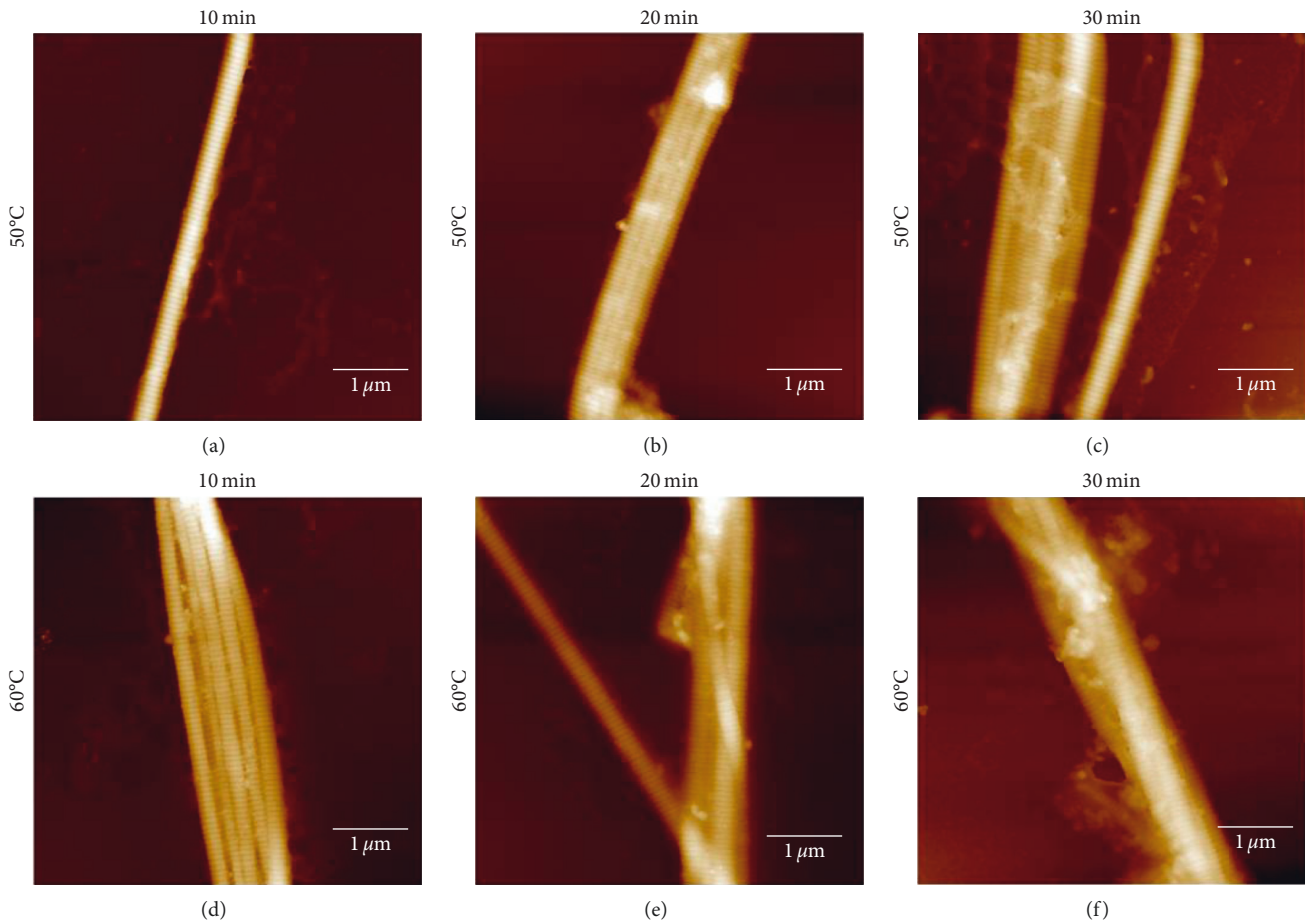

Figure 6: Continued.

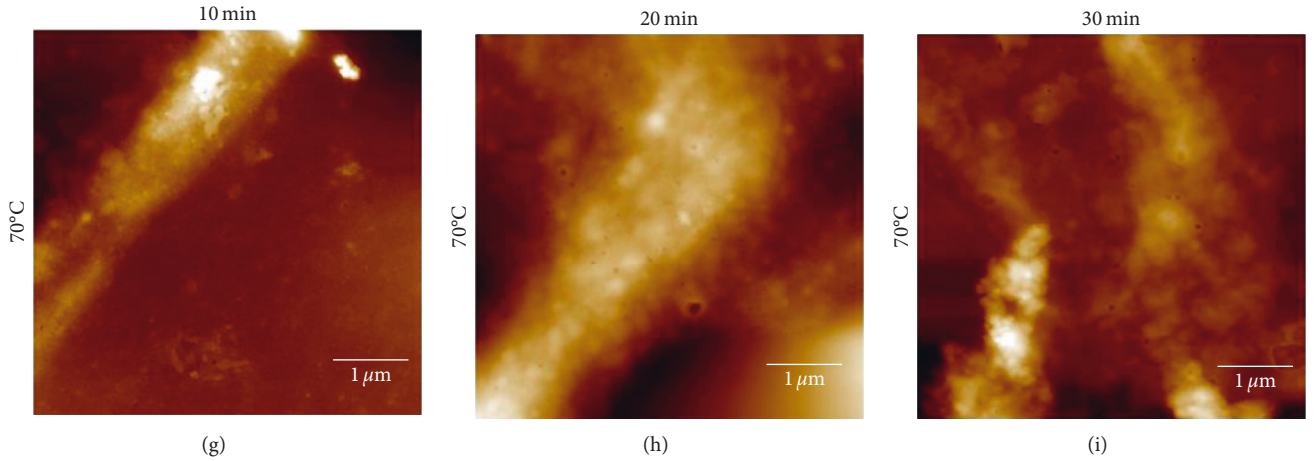

Figure 6: Typical AFM height images of collagen fibers heated in a water bath at (a–c) 50°C, (d–f) 60°C, and (g–i) 70°C for 10, 20, and 30 min, respectively.

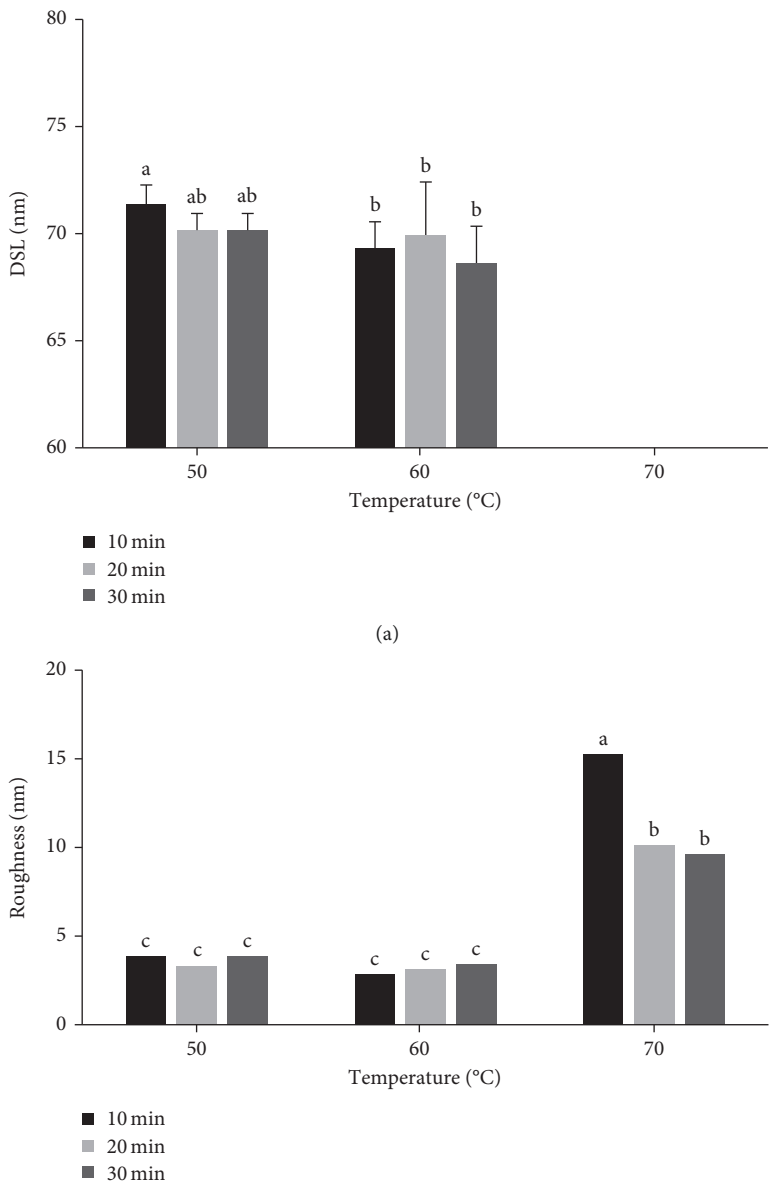

Figure 7: DSL (a) and roughness (b) of collagen fibrils under different water bath temperatures and times. a, b, and c values in the row and column; entries with the same superscript are not significantly different ($p \geq 0.05$).

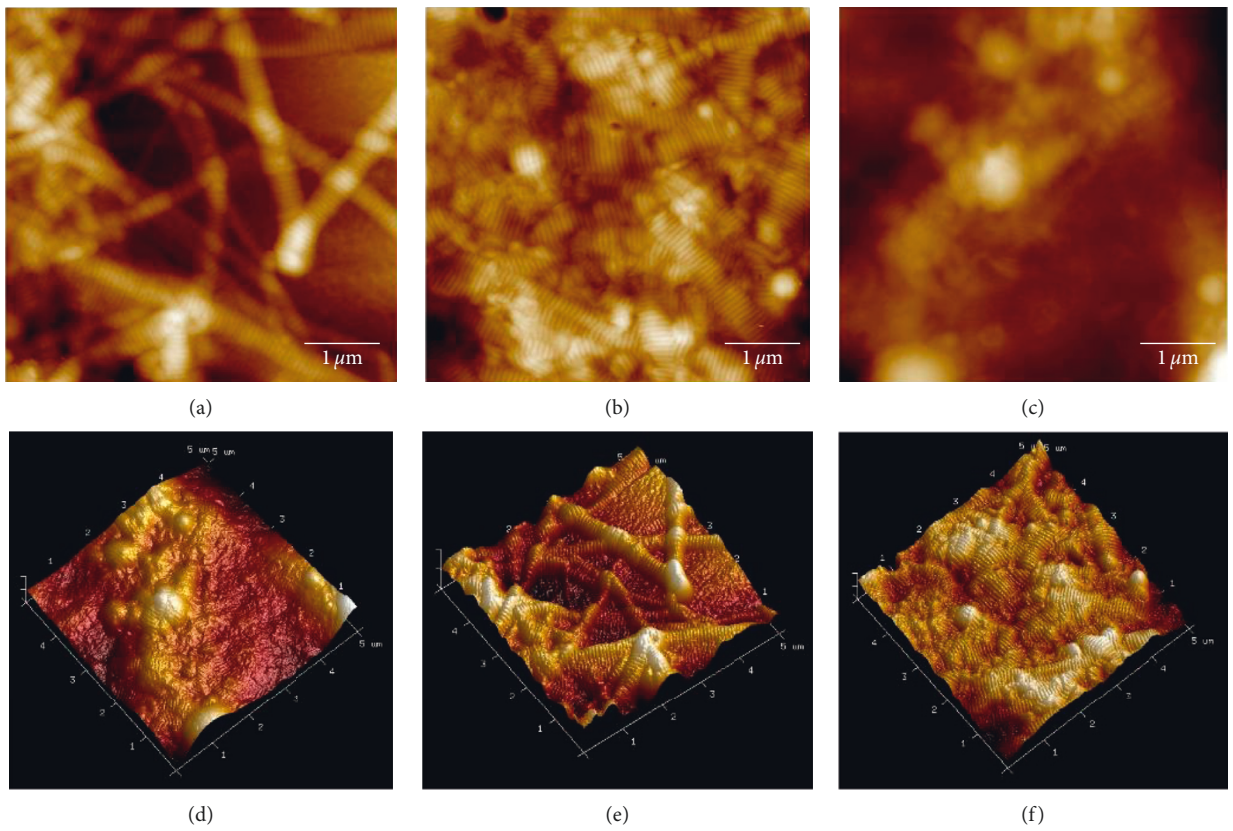

Figure 8: Typical AFM height 2D (upper) and 3D (lower) images of collagen fibrils treated by acid-base soaking. (a–c) Samples soaked in acid solutions at pH 3 for 7.5, 15, and 25 h, respectively; (d–f) 3D images of (a–c), respectively.

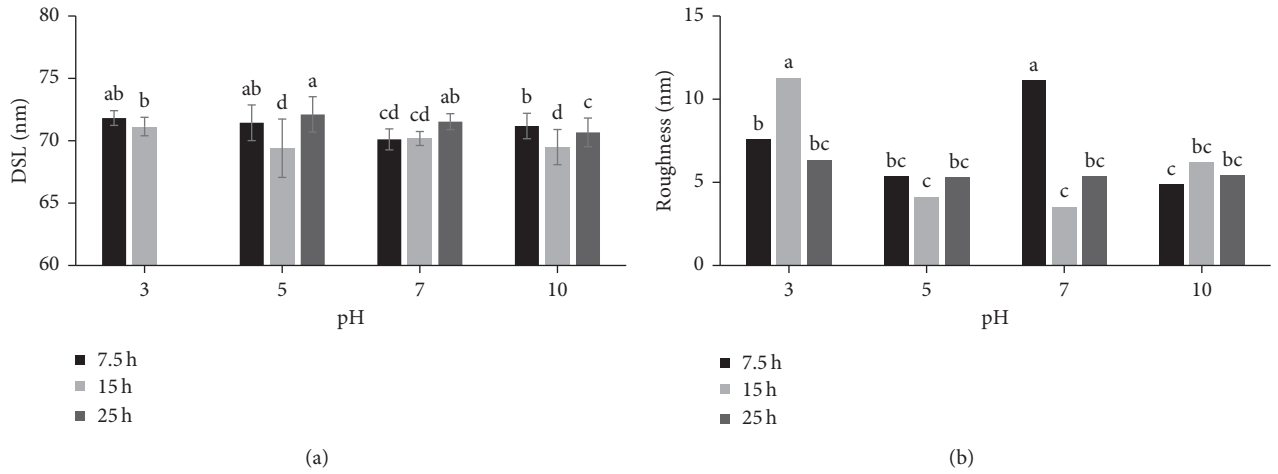

Figure 9: DSL (a) and roughness (b) of collagen fibrils soaked in acidic and alkaline solutions. a, b, c, and d values in the row and column; entries with the same superscript are not significantly different ($p \geq 0.05$).

disappeared at pH 3 for the 25-hour group and there was a certain degree of increased length in acidic and alkaline environments compared with pH 7 [27]. Overall, the ultrastructure of fibers displayed the most noticeable changes at pH 3, and DSL was maximal at pH 5 for the 15-hour group. When samples were incubated for 7.5 h under different pH values, the variation of DSL was not apparent, but at pH 3, fibrils had presented chaotic arrangements. This suggested that a strong acid destroyed the cross-links among fibrils so that it disordered the alignment of the fibrils and even damaged the internal structure; there was essentially no effect on DSL. Local fibrils had been hydrolyzed during immersion for 15 h (Figure 8(b)); at pH 3, periodic structure disappeared in a wide range; therefore, DSL could not be measured for the 25 h incubation.

Figure 9 gives the roughness values of samples incubated in solutions where pH values were 3, 5, 7, and 10. For the 25-hour group at pH 3, the ultrastructure of collagen fibrils

disappeared, indicating that the collagen fibrils had been hydrolyzed. It could be noticed that roughness tended to be stable because of a lot of processing and reached a maximum for the 15-hour group at pH 3.

4. Conclusions

Ultrasonic oscillation, microwave heating, water bath cooking, and acid-base soaking had complex effects on the internal structure of collagen fibrils of Qinchuan cattle tendons. As a result of ultrasonic oscillation, DSL values after 20 min were generally greater than after 10 min, as were roughness values. The regular cross-striated fibril structure disappeared, along with disintegration of the protein structure, after microwave heating at 700 W for 10 and 15 min. DSL values became gradually shorter at 50°C; they became shorter within 20 min, at 60°C. After 20 min at 70°C in a water bath, fibrils had become gelatinized. The cross-links between fibrils disappeared at pH 3 and fibrils were even hydrolyzed by acid-base soaking.

The ultrastructure of fibrils and internal connections were modified by different treatments. Although fibril structure could not be changed by ultrasonic treatment, the other three treatments led to the denaturation of fibrils and protein by strengthening the reaction intensity. This study is exploratory and tentative, with less pertinent reports and research on fiber level particularly. It elaborates ultrastructural changes in the collagen fibrils through four different treatments qualitatively and quantitatively; compared with other methods, it is more detailed and accurate. The present technology provided an extremely useful direction and guidance for meat quality evaluation and microscopic measurement. This study was mainly engaged at the fiber level and expected to further studies such as those on fiber gels in the future [28].

Data Availability

No supplemental data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Authors' Contributions

Guixia Li and Yunfei Wan contributed equally to this work.

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References

[1] M. Liu, J. L. Li, N. H. Dan, and W. H. Dan, "Extraction and characterization of collagen fiber from bovine tendon," *China Leather*, vol. 42, no. 1, pp. 19–22, 2013.

[2] O. Latinovic, L. A. Hough, and H. Daniel Ou-Yang, "Structural and micromechanical characterization of type I collagen gels," *Journal of Biomechanics*, vol. 43, no. 3, pp. 500–505, 2010.

[3] P. Berillis, N. Panagiotopoulos, V. Boursiaki, I. T. Karapanagiotidis, and E. Mente, "Vertebrae length and ultra-structure measurements of collagen fibrils and mineral content in the vertebrae of lordotic gilthead seabreams (*Sparus aurata*)," *Micron*, vol. 75, pp. 27–33, 2015.

[4] M. F. Paige, J. K. Rainey, and M. C. Goh, "A study of fibrous long spacing collagen ultrastructure and assembly by atomic force microscopy," *Micron*, vol. 32, no. 3, pp. 341–353, 2001.

[5] A. Stylianou, D. Yova, E. Alexandratou, and A. Petri, "Atomic force imaging microscopy investigation of the interaction of ultraviolet radiation with collagen thin films," in *Nanoscale Imaging, Sensing, and Actuation for Biomedical Applications X*, Vol. 8594, San Francisco, CA, USA, 2013.

[6] K. E. Kadler, D. F. Holmes, J. A. Trotter, and J. A. Chapman, "Collagen fibril formation," *Biochemical Journal*, vol. 316, no. 1, pp. 1–11, 1996.

[7] J. Davidovits, "The quaternary and fibrillar structure of native collagen," *Journal of Theoretical Biology*, vol. 12, no. 1, pp. 1–11, 1966.

[8] C. M. da Silva, E. Spinelli, and S. V. Rodrigues, "Fast and sensitive collagen quantification by alkaline hydrolysis/hydroxyproline assay," *Food Chemistry*, vol. 173, pp. 619–623, 2015.

[9] C. Ding, M. Zhang, and G. Li, "Effect of cyclic freeze–thawing process on the structure and properties of collagen," *International Journal of Biological Macromolecules*, vol. 80, pp. 317–323, 2015.

[10] X. Cheng, M. Zhang, B. Xu, B. Adhikari, and J. Sun, "The principles of ultrasound and its application in freezing related processes of food materials," *Ultrasonics Sonochemistry*, vol. 27, pp. 576–585, 2015.

[11] D. Knorr, M. Zenker, V. Heinz, and D. U. Lee, "Applications and potential of ultrasonics in food processing," *Trends in Food Science and Technology*, vol. 15, no. 5, pp. 261–266, 2004.

[12] H. J. Chang, X. L. Xu, C. B. Li, M. Huang, D. Y. Liu, and G. H. Zhou, "A comparison of heat-induced changes of intramuscular connective tissue and collagen of beef semitendinosus muscle during water bath and microwave heating," *Journal of Food Process Engineering*, vol. 34, no. 6, pp. 2233–2250, 2011.

[13] M. Regier, "Food technologies: microwave heating," in *Encyclopedia of Food Safety*, vol. 3, pp. 202–207, Academic Press, Cambridge, MA, USA, 2014.

[14] J. Sherma, D. John, and F. H. Larkin, "Atomic force microscopy (AFM)," *Journal of AOAC International*, vol. 88, no. 6, pp. 133A–140A, 2005.

[15] S. Li and L. Liao, "Development of SPM quantitative micromorphology analysis software," *Journal of University of Science and Technology Beijing*, vol. 6, no. 2, pp. 136–138, 1999.

[16] N. C. Santos and M. A. Castanho, "An overview of the biophysical applications of atomic force microscopy," *Biophysical Chemistry*, vol. 107, no. 2, pp. 133–149, 2004.

[17] A. F. Raigoza, J. W. Dugger, and L. J. Webb, "Review: recent advances and current challenges in scanning probe microscopy of biomolecular surfaces and interfaces," *ACS Applied Materials and Interfaces*, vol. 5, no. 19, pp. 9249–9261, 2013.

[18] J. Zhu, L. H. Guo, G. D. Wang, and W. Q. Ouyang, "Application of atomic force microscopy in ultrastructure and biomechanics of cells and biomacromolecules," *Journal of Medical Biomechanics*, vol. 27, no. 3, pp. 355–360, 2012.

[19] S. Strasser, A. Zink, M. Janko, W. M. Heckl, and S. Thalhammer, "Structural investigations on native collagen type I fibrils using AFM," *Biochemical and Biophysical Research Communications*, vol. 354, no. 1, pp. 27–32, 2007.

[20] A. Sikes, E. Tornberg, and R. Tume, "A proposed mechanism of tenderising post-rigor beef using high pressure-heat treatment," *Meat Science*, vol. 84, no. 3, pp. 390–399, 2010.

[21] H. J. Chang, X. L. Xu, G. H. Zhou, C. B. Li, and M. Huang, "Effects of characteristics changes of collagen on meat physicochemical properties of beef semitendinosus muscle during ultrasonic processing," *Food and Bioprocess Technology*, vol. 5, no. 1, pp. 285–297, 2009.

[22] H. J. Chang, Q. Wang, C. H. Tang, and G. H. Zhou, "Effects of ultrasound treatment on connective tissue collagen and meat quality of beef Semitendinosus muscle," *Journal of Food Quality*, vol. 38, no. 4, pp. 256–267, 2015.

[23] R. D. Warner, C. K. McDonnell, A. E. D. Bekhit et al., "Systematic review of emerging and innovative technologies for meat tenderisation," *Meat Science*, vol. 132, pp. 72–89, 2017.

[24] Z. Q. Liu, F. Y. Tuo, L. Song et al., "Action of trypsin on structural changes of collagen fibres from sea cucumber (*Stichopus japonicus*)," *Food Chemistry*, vol. 256, pp. 113–118, 2018.

[25] H. L. Xiao, S. Q. Sun, Q. Zhou, X. F. Pang, and G. P. Ca, "Two-dimensional correlation analysis of FTIR spectrum for collagen during variable temperature denaturing process," *Chinese Journal of Atomic And Molecular Physics*, vol. 20, no. 2, pp. 211–218, 2003.

[26] H. J. Ma and D. A. Ledward, "High pressure/thermal treatment effects on the texture of beef muscle," *Meat Science*, vol. 68, no. 3, pp. 347–355, 2004.

[27] K. Matmaroh, S. Benjakul, T. Prodpran, A. B. Encarnacion, and H. Kishimura, "Characteristics of acid soluble collagen and pepsin soluble collagen from scale of spotted golden goatfish (Parupeneus heptacanthus)," *Food Chemistry*, vol. 129, no. 3, pp. 1179–1186, 2011.

[28] M. C. de Moraes and R. L. Cunha, "Gelation property and water holding capacity of heat-treated collagen at different temperature and pH values," *Food Research International*, vol. 50, no. 1, pp. 213–223, 2013.