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Review

A Review on Silk Fibers and Their Medical Applications

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Abstract

This mini-compilation study included the chemical structure, mechanical, thermal, and dimensional properties of silk fiber, its production process, pre-treatment, and biomedical applications from various experimental studies, which are compiled and summarized. The silk fiber should have a degumming process before using biomedical applications. The 25% concentration for Na_2CO_3 in ethanol solution (80%) as a coagulant chemical with a salt such as LiB_2 (9 M) at a temperature of 98°C for 45 minutes at pH between 6 and 7 should be applied for the degumming process of silk fiber. It has some biomedical applications such as artificial veins and surgical sutures. Its biomedical applications can be studied experimentally by changing manufacturing processes and their process parameters in the future.

Keywords
Silk fibers; chemical and biomechanical properties; pre-treatment (degumming) processes; manufacturing processes; biomedical applications

1. Introduction

The purpose of this review study about silk fibers provide a general perspective on their chemical structure, pre-treatment processes, mechanical properties, production methods, and biomedical textile applications. They can be produced from silkworms, mites, some insects (including spiders), and many arthropods by extraction [1-30]. The spinning process has a direct effect on the molecular arrangement of silk. Their quality factors are insect type, molecular weight, amino acid type and ratio, crystal chain type, coagulant chemical type, the viscosity of the solution, pH, concentration, temperature, and time [1-30]. A graphic abstract summarizing the mini-review article is presented in Figure 1.

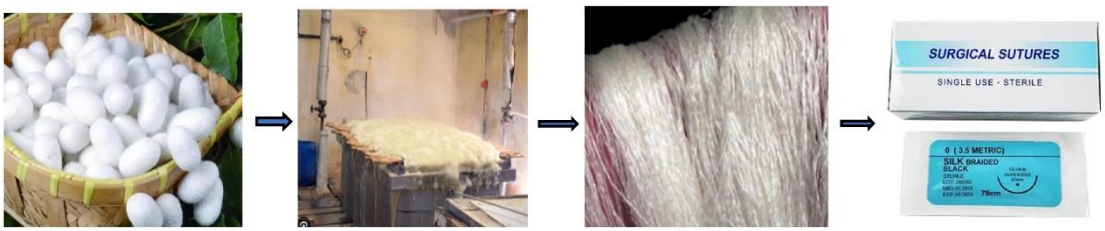

Figure 1 a) raw silk fiber (cocoon), b) degumming process, c) degumming silk fiber, d) biomedical application.

1.1 Chemical Structure and Mechanical Properties of Silk Fibers

The chemical structure of silk fibers is a protein-based chemical structure secreted by the Bombyx mori silkworm. Sericin includes the fibroin protein, which consists of fibrils. A fibroin fibril consists of a heavy structure (between 325 and 350 kDa) and light (approximately 25 kDa). They are connected by a single disulfide bond in the α or β crystal chain arrangement in their chemical structure [1, 3-8, 12, 18, 19, 26-30]. Their heavy crystalline chain consists of 12 hydrophobic repeats connected by hydrophilic linkers. Silk fibroin has two different configurations, silk I and silk II, and has a dimorphic structure. Silk I is characterized by an α helix. Silk II, on the other hand, is characterized by its anti-parallel β-sheet nanocrystal conformation [1, 3, 8, 14, 26-30]. The chemical structure of silk fibers consists of between 12 and 19 amino acids, mainly glycine (45%), alanine (30%), and serine (12%). These amino acid structures cause hydrophobicity. Van der Waals and hydrogen bonds connect short chains and are hydrophilic [1-5, 9, 15, 16, 24, 28, 30]. The structure of Bombyx mori silk fiber is presented in Figure 2 [1].

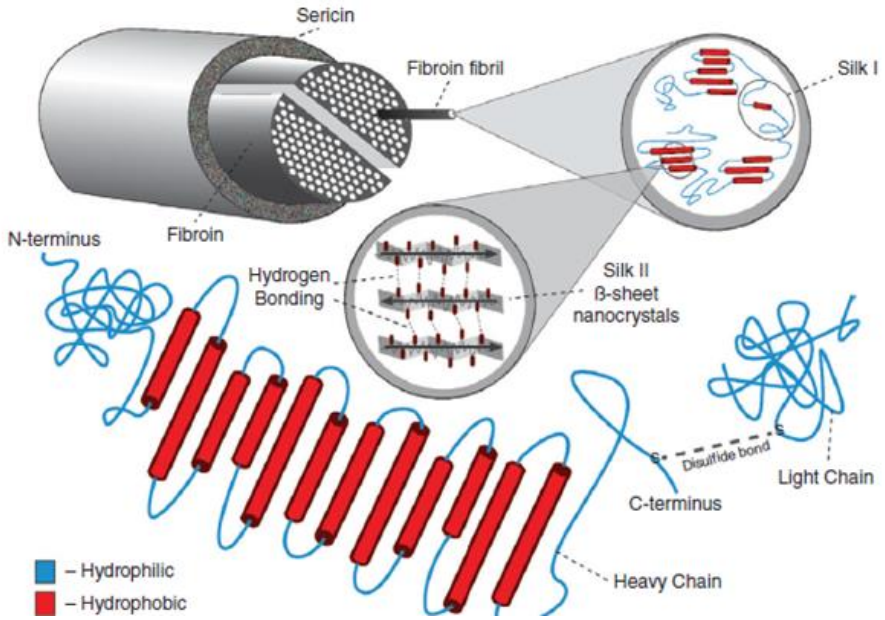

Figure 2 The structure of Bombyx mori silk fiber [1].

β-sheet formation in silk fibers occurs in the temperature range of 205°C to 245°C for B. mori-type fibroin or the range of 210°C to 225°C for N. mori-type fibroin [5]. The β-sheet nanocrystal structures of silk fibers are in sheet form and generally have polar-antiparallel positions. They have a shorter chain length thanks to glycine in the antiparallel position. Thus, they have a more linear chemical chain. Their glycine and alanine groups support their crystalline. Serine and tyrosine transform the crystalline structure into an amorphous structure. Moreover, they have a more polar chemical structure thanks to the presence of glycine. They have a parallel or antiparallel polymer chain configuration depending on their polar chemical groups. They have a tensile strength of 3.8 GPa and 4% elongation at break for antiparallel positioning, while they have a tensile strength of 2.5 GPa and 9% elongation at break for parallel positioning. Their chemical structures consist of carbon, oxygen, nitrogen, and hydrogen atoms [4, 5, 24, 28-30]. They have high tensile strength and toughness values thanks to their β-crystal chain arrangement [2, 4, 5, 18, 21, 23, 24, 26-30]. They have differences in their morphological properties. These differences are structural changes along its density, length, sericin content, filament size, longitudinal and cross-sectional shape, degree of crystallinity, and orientation [4-8, 12-14, 16-21, 24, 26-30]. The density of B. mori silk fiber is 1.34 g/cm^3. The density of degumming silk fiber is 1.27 g/cm^3. The density of spider silk fiber is 1.31 g/cm^3 [23, 24]. Table 1 presents a range of experimental studies on the mechanical properties of silk fiber [1, 3-8, 10, 11, 13, 16-19, 22-24].

Table 1 Various experimental studies on the mechanical properties of silk fiber [1, 3-8, 10, 11, 13, 16-19, 22-24].

Silk fiber type	Modulus of elasticity (GPa)	Tensile strength (MPa)	Percent breaking elongation (%)	Source
B. mori (raw, and degumming process)	15-17, 5-12	500, 610-690	19, 4-16	[1]
B. mori (raw)	5	400	15	[3]
B. mori (raw, and degumming process)	17.9-12.4	200-530	21-18	[4]
B. mori (degumming process) A. diadematus MA silk (degumming process) A. diadematus Flag silk (degumming process)	None, None, None	600, 1100, 500	18, 27, 270	[5]
B. mori (raw)	17.4	231	18	[6]
B. mori (raw)	17.4	231	22	[7]
B. mori (degumming process with and Na_2CO_3(100°C), ethanol(100°C, 60°C, 75°C))	8.1, 8.5-10.5, 9.8-14.6, 8.9-10.5	309, 318-502, 521-533, 394-471	13, 11-20, 15-19, 11-29	[8]
B. mori (raw, and degumming process with FA (as spun and drawn) and TFA (as spun and drawn))	100.62 (g/den), 263.26 (g/den), 315.65 (g/den), 244.40 (g/den), 362.20 (g/den)	5.25 (g/den), 2.56 (g/den), 8.53 (g/den), 2.38 (g/den), 8.04 (g/den)	25.89, 2.54, 29.34, 1.33, 18.12	[10]
B. mori (raw, and degumming process with hot water, 15% soap, 15% citric acid, and 30% citric acid)	8.3, 7.9, 7.2, 7.4, 6.9	422, 394, 250, 507, 423	13.6, 13.0, 18.1, 20.0, 17.4	[11]
B. mori (raw), and Spider silk (Nephila edulis-degumming)	None, None	400, 1150	26.0, 40.0	[13]
B. mori (raw, and degumming process)	None, None	2.9 (g/den), 3.2 (g/den)	22.4, 23.5	[16]
B. mori (degumming process), and Spider silk (Nephila edulis- degumming process)	None, None	500, 1300	15, 40	[17]
B. mori (raw with 2, 3, 4, 6 as draw-down ratio)	6.7, 10.4, 13.2, 15.2	120, 190, 200, 390	4.8, 4.7, 15.7, 32.1	[18]

B. mori (degumming process with PEG30(8%) + Ca(16%, 8%), Ethanol(80%) + Acetic acid(0.2 M) + (16%, 4%), None Ca(4%))	None, None, None, None, None, None	190, 150, 90, 200, 100, 60	10, 20, 15, 60, 23, 20	[19]
B. mori (raw, and degumming process)	None, None	250, 450	23, 18	[22]
B. mori (raw, and degumming process), and spider silk	9-10, 15-17, 11-13	510, 610-690, 875-972	20-24, 4-16, 17-18	[23]
B. mori (degumming process), β-sheet crystallites, β-sheet crystallites, Spider silk (Nephila clavipes), Spider silk (Nephila edulis), Spider silk (Araneus)	10-17, 16-18, 22.6, 10.9, None, 10	300-740, None, None, 875, 1300, 1100	4-26, None, None, 16.7, 38, 27	[24]

1.2 Degumming Process for Silk Fibers

"Degumming" which is the pre-treatment process of silk, is carried out by heating the raw silk. The purpose of the degumming process is to remove the sericin part of the silk fiber from the fibroin part by taking advantage of its water solubility and preventing various complications, especially in medical applications. [1, 3-5, 8-13, 17-20, 24, 29, 30]. It is extremely important and directly affects and changes their mechanical properties. [1, 4, 5, 8-13, 14, 18-21, 23, 24, 26-30]. Table 2 presents various experimental studies on the degumming process of silk fiber [8-21].

Table 2 Various experimental studies on the degumming process of silk fiber [8-21].

Silk fiber type	Degumming chemical	Concentration (%, M, g/L or mM)	Temperature (°C)	Time (minute)	Liquor ratio (1:X)	Source
B. mori (raw)	Na_2CO_3, and SDS	25(%), 25(%)	60-100	15-90	None	[8]
B. mori (raw)	Na_2CO_3, and LiB_2 (salt)	0.02(M)-0.04(M), 9.3(M)	70	20, 40, 60, 80, 150, 180	None	[9]
B. mori (raw)	$CH_3(CH_2)10CH_2$ $(OCH_2CH_2)_nOSO_3Na$, and Na_2CO_3	25(%), 25(%)	80	10	1:100	[10]
B. mori (raw)	$C_6H_8O_7$, Marseilles soap, Na_2CO_3, Noigen HC nonionic detergent, and EDTA	15(%), 30(%), 15(%), 1.5(%), 0.05(%), 0.05(%)	98	30	1:20, 1:30	[11]
B. mori (raw)	Salt	0.1(g/L), 1.1(g/L)	70-98	20-90	1/1, 1/2	[12]
B. mori (raw), and Nephila edulis (raw)	Na_2CO_3, soap, LiB_2, and PEG	0.5(%), 9(M), 5(%), 10(%), 15(%)	4-25	30	None	[13]
B. mori (raw)	Boiling H_20	100(%)	65	2	None	[14]
B. mori (raw), and A. pernyi (raw)	Soap, boiling H_2O, Na_2CO_3, and Na_2SiO_3	0.5(%)	98	60	None	[15]
B. mori (raw)	Soap, and Na_2CO_3	5(g/L), 2(g/L)	95-98	45	None	[16]
B. mori (raw), and Nephila edulis (raw)	$NaHCO_3$	1(%)	25	None	None	[17]
B. mori (raw)	$(NH_4)_2SO_4$	30(%)	25	None	6.5-7.0	[18]
B. mori (raw)	PEG30, ethanol, and acetic acid	30(%), 80(%), 0.2(M)	None	None	None	[19]
B. mori (raw)	$C_6H_{11}N_2Cl$, Na_2CO_3, and Na_2EDTA	10(%), 50(mM), 50(mM)	95	None	None	[20]
B. mori (raw)	Na_2CO_3	0.4(g/L), 1.1(g/L)	None	60	None	[21]

It takes place in a too-weak acidic aqueous solution that breaks down the serine amide bonds and ensures that only the fibroin fibers remain intact [1, 4, 14, 24]. Thus, it has higher toughness than a high-performance fiber such as para-aramid (Kevlar) [24]. As the concentration of the coagulant chemical such as Na_2CO_3 at 70°C (0.1 M to 0.4 M concentration) and process time (20 minutes to 90 minutes) increases, the removal of degumming increases, and fiber diameter (µm) decreases in the degumming process. There is also no significant difference in serine removal between 70°C and 98°C [9, 11, 12]. In degumming and wet spinning processes, diluted Na_2CO_3 is commonly utilized however repeatability is relatively low. Urea is also used and has higher repeatability. Sodium dodecyl sulfate, lithium bromide, calcium dichloride, ethyl alcohol, water, polyethylene glycol, polyethylene oxide, soaps, orthophosphoric acid, formic acid, citric acid, hexafluoroacetate hydrate, chloroauric acid, 1,1,1,3,3,3-hexafluoro-2-propanol, 2-6,10 hexafluoroacetone, trifluoroacetic acid, 1-ethyl-3-methylimidazolium chloride, ethylenediaminetetraacetic acid, ethyl acetate, acetone, hexanes, and water are suitable for coagulant chemicals. Thus, the use of salt such as LiB_2 in a protein-based fiber such as silk fiber triggers the transformation from liquid to solid phase for the dimensional stability of the protein-based molecular conformation and the effect of pH, which provides a too-weak acidic environment close to neutral that triggers these chemical reactions, are extremely important and sensitive [1, 3-6, 8-13, 18-21, 24-30]. The use of methanol is more suitable for their smooth cross-sections. Acetonitrile provides easy water solubility, amorphous structure formation, and light scattering [20]. Experimental study on the degumming process of silk fiber included 100°C temperature and 30 minutes were the best values for preserving its mechanical properties and dimensional stability with Na_2CO_3 and sodium dodecyl sulfate at 0.25% concentrations [8]. Another experimental study included scanning electron microscope (SEM) images, which revealed partial fibrillation on the surface. Furthermore, there was a significant increase in percent elongation at break (%) at 280°C in the Differential Scanning Calorimeter (DSC) thermal test. In the thermogravimetric analyzer (TGA) mass loss test, 25.4% mass loss was observed in the sample pre-treated with a 30% concentration of citric acid [11]. Another degumming study included only the molecular weight increased from 86% to 91% in heat-treated silk fiber. That was a 5% increase was achieved [16].

1.3 Manufacturing Process for Silk Fibers

Bombyx mori is the most commonly used type of silkworm in silk fiber production. Moreover, silkworms of the types Araneus diadematus, Antheraea pernyi, Antheraea yamamai, and Antheraea mylitta, Nephila clavipes, and Nephila edulis are also used, too [1-24, 26-30]. A silkworm can continuously produce between 700 m and 1500 m for its length and between 7 µm and 40 µm for its diameter [4, 5, 7, 12, 14, 28]. Silk fiber production takes place in 4 stages. These stages are cocoon drying, cooking, wrapping, and re-wrapping [16]. The wet spinning process is applied in the silk fiber production [10, 18-20, 23]. It can also produced at between 15%, and 40% concentration with a coagulant chemical such as H_2O, CH_3OH, C_2H_5OH, $C_6H_5CH_3$, $CaCl_2$, and LiB_2 for 90 minutes as its process time, too [4, 5]. Azide, cyanogen bromide, diazo, or glutaraldehyde are viable options for enhancing covalent linking in silk fibers [5]. Moreover, the process can also be employed to orient the fibroin fibers with air space before the wet process [5, 6, 28]. The air gap is usually 50 mm [18-20, 30]. Dry, dry-jet wet spinning, electrospinning, and biomimetic spinning methods can also be used [5, 18-20, 23, 24, 27-30].

The drawing speed and rate are extremely important in silk fiber production. As drafting speed and ratio increase, the mechanical properties of silk fibers also improve significantly thanks to molecular orientation and packing [18-20, 28]. Hexafluoroacetone or trifluoroacetic acid is also used as an auxiliary coagulant chemical to increase protein concentration in the wet spinning process production of silk fibers. Moreover, methanol and ethanol can also be used because they are economical but toxic. Thus, they are not recommended as coagulant chemicals [18]. Another experimental study on the production of silk fibers included the speed of the feed roller was 7.8 m/min with 50 rpm as a cycle [28]. Their drawing ratio was changed between 2 and 6 [18-20]. As the draft rate increased, the diameter of the silk fiber decreased from 40 µm to 10 µm [5, 6]. As the concentration of the coagulant chemical increased and, the loop form changed from noose to X-form, the silk fiber exhibited a brittle fracture mechanism. [19, 21, 22]. Moreover, raw and degummed types were increased by 350% and 250% respectively, the tensile strength of silk fiber in the slip knot form. Their tensile strengths were decreased by approximately 110% in the double-turned slip knot form [22]. In an experimental study, crystallite size (nm) and degree of orientation were examined by changing the drawing ratio between 1 and 27. The effect of the drawing ratio on the degree of orientation was not observed [24].

1.4 Biomedical Applications for Silk Fibers

Biomedical applications for silk fibers are controlled drug delivery systems, artificial vascular grafts, artificial heart valves, artificial lenses, artificial skin, artificial teeth, artificial joints, artificial ligaments, artificial tendons, artificial bones, artificial stents, artificial surgical sutures, artificial masks, and artificial wound dressings [1-3, 5, 8-10, 12, 20, 21, 23-30]. The reasons for using silk fibers in medical applications are ease of processing, biocompatibility, non-biodegradable, non-toxic, low immunogenicity, low risk of infection, high dimensional stability, high tensile strength, high compressive strength, high radial strength, and high modulus of elasticity. They also support the adhesion and growth of collagen tissues produced by fibroblast cells in the body over time in silk fiber-based medical products [1, 2, 5, 9, 10, 15, 23, 25-30].

Medical textiles utilizing of silk fibers can encompass a variety of forms, such as scaffolds, films, hydrogels, and nanoparticles. These textiles can be manufactured using braiding, weaving, knitting, non-woven methods, and electrospinning. Combinations of these methods and production using 3D printers are also viable options for creating medical textiles [2, 5, 18-20, 23, 24, 26-30]. Braided structures have a higher modulus of elasticity, higher tensile strength, and lower percent elongation at break-to-knitted structures [5, 24]. That is, they support tissue-graft interface development. Additionally, they must be subjected to physical pre-treatment processes, such as a chemical process with the help of various degumming chemicals or a plasma process with oxygen, before silk fibers can be converted into medicinal products [23].

Biomechanical properties of silk fibers, such as tensile strength, degradation rate, and surface morphology, vary depending on the type of chemical used and degumming process parameters thanks to coated with natural biopolymers. Moreover, the molecular weight of the silk fibers usually changes due to their pore size, number of pores, and crystallinity change. The coating chemicals of silk fiber are generally protein-based, cellulosic-based, and synthetic-based chemicals.

These are hydrogel, chitosan, sodium hydroxide, titanium hydroxide, vinyl phosphate, polypyrrole, cadmium sulfide, polyethylene oxide, horseradish peroxidase, carbodiimide, glucose

oxidase, 1,2-cyclohexanedione, arginine-glycine-aspartic acid, parathyroid hormone, and bone morphogenetic protein-2 [5, 6, 23, 27]. Saos-2 canalter cell adhesion and proliferation, including osteoblasts, tenocytes, hMSCs, and fibroblasts. Amino and carboxyl groups become reactive thanks to these coating chemicals of the silk fibers. Thus, an improved tissue-graft interface is provided as it supports high adhesion thanks to the tyrosine chemical structure found in the silk fiber at a rate of >5% [23]. An experimental study on the artificial surgical thread made of silk fibers determined that artificial surgical sutures made of multifilament silk fibers had a between 5 and 8 times higher risk of infection than their monofilament types. This situation was because microorganisms adhered to the spaces between multifilaments. Moreover, monofilament was easier to knot and had lower tissue reactivity [25]. When transforming silk fiber from the noose loop form to the X-loop form, there was a higher rate of increase in toughness (approximately 150%) while the rate of decrease in tensile strength was lower (approximately 200%). Because the X-type loop form of the silk fiber had more friction force [21]. The type of yarn used, yarn structure, biological, chemical, and mechanical properties of the yarns, production method, size, and length were important design criteria for artificial surgical sutures. UPS criteria were available for artificial surgical sutures. The gaps between the multifilaments that make up silk fibers encouraged microorganism proliferation. Thus, the risk of infection increased. Moreover, the cross-section of the silk fibers was smooth, compact, and flexible. Thus, they prevented the formation of bacteria thanks to their porosity. It was determined that their mechanical properties were suitable for artificial surgical thread applications [25]. Design criteria for artificial vascular applications were included in an experimental study on artificial vascular grafts from silk fibers. They had to resist high and low blood pressure values and flexibility. Also, they had to be antithrombotic, have a blood-compatible lumen, be mechanically robust to maintain physiological blood pressure, have easy availability, compatibility with vascular cells, have minimal immunogenicity, and tunable biodegradability. Moreover, they had to allow remodeling of the reparative artificial vascular graft before biodegradability, and cost-effectiveness. In conclusion, their biological and mechanical properties were suitable for artificial vascular grafts with a diameter of <6 mm. Moreover, biological complications such as ease of use, long-term patency, resistance to acute thrombosis, stenosis and aneurysm formation, immune reaction, neo-tissue formation, and general restructuring must be investigated in the in-vivo environment [27]. An experimental study on artificial vascular grafts from silk fibers produced had double-bed, raschel-knitted textile fabrics. As a result, they had suitable mechanical properties. Additionally, tearing should be reduced by reducing the number of intersection points of the threads. Moreover, sufficient force values and high loosening problems were at the edges of the knitted textile fabric. In conclusion, artificial vascular grafts with a diameter of ≥6 mm did not exhibit various intrabody complications [28]. An experimental study on artificial bone made of silk fibers included the initial stage of the degumming process, which utilized a concentration of 9.3 M lithium bromide chemical at 55°C for 5 hours. Following this, the bones were dried at room temperature. The artificial bones were fashioned into 3D porous structures in cylindrical and disc forms through cold molding. Subsequently, they underwent freezing at -20°C for 4 hours followed by further freezing at -80°C for 1 hour. Chemical surface modification was applied with methanol at a concentration of 99.98% for 1 hour. In conclusion, the study observed osteogenic differentiation. Moreover, their biological and mechanical properties were high and were suitable for artificial bone applications [29].

It was suggested that silk fibers can be utilized in artificial teeth applications after following the application of the degumming process [30].

2. Conclusions

Their biomechanical, chemical, thermal, crystallinity, mass, and dimensional stability properties can be changed thanks to differences in the chemical structure of various amino acid groups and particles. A chemical or physical pre-treatment process is applied to remove fully sericin before biomedical applications such as artificial veins and stitches. This process has a certain temperature (between 25°C and 100°C), duration (between 0.5 hours and 5 hours), liquor ratio (between 1:10 and 1:50), draw speed (between 2 m/min and 8 m/min), and draw ratio (between 1 and 27) in within a slightly acidic environment (between 6.5 and 7 for pH). Additionally, coagulant chemicals such as CH_3OH or LiB_2 (between 5% and 10% for their concentrations), and salt chemicals such as Na_2CO_3 or $(NH_4)SO_4$ (30% for their concentrations) are also utilized as part of the chemical pre-treatment process. Those concentrations should be applied to activate their highly reactive R-dependent -NH_2 and -COOH. Their basic dimensional properties, such as size, weight, and biomechanical analyses should be determined thanks to their mechanical strengths in their biomedical applications. Also, their surface morphologies should be determined by SEM analysis in their biomedical applications. Their chemical, thermal, crystallinity, and mass characterizations should be determined by such as EDX, FT-IR, DSC, XRD, and TGA, respectively, in their biomedical applications.

Author Contributions

Alhayat Getu Temesgen determined the subject of the mini-review study. He also scanned and interpreted some of the relevant articles. Ömer Fırat Turşucular scanned and interpreted some of the relevant articles. Elif Dicle Turşucular scanned and interpreted some of the relevant articles.

Competing Interests

The authors have declared that there have no competing interests exist.

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