J. Mar. Biosci. Biotechnol. 2021, p. 28 - 47 Vol. 13, No. 1 [Research Paper]

http://doi.org/10.15433/ksmb.2021.13.1.028 ISSN 2383-5400 (Online)

# Recent advances of pectin-based biomedical application: potential of marine pectin

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(Received 16 May 2021, Revised 28 May 2021, Accepted 8 June 2021)

**Abstract** Pectin is a natural polysaccharide and biopolymer that serves as a structural component of plant tissues' primary cell walls. Pectin is primarily composed of D-galacturonic acid linked by α-1, 4-glycosidic linkage and is further classified by the ratio of esterified galacturonic acid groups known as degree of esterification (DE). Pectin that contains more than half of its carboxylate units as methyl esters is known as a high methyl (HM) ester. Conversely, pectin that has less than half of its carboxylate units as methyl esters is known as a low methyl (LM) ester. Pectin has various bioactive properties, including anticancer, anti-inflammatory, antioxidant, antidiabetic, anticholesterol, antitumoral, and chemopreventive properties. Moreover, pectin is a useful biopolymer in biomedical applications. Biomedical engineering, which is founded on research aimed to improve the quality of life using new materials and technologies, is typically classified according to the use of hydrogels, nanofiber mats, and nanoparticles. This paper reviews the progress of recent research into pectin-based biomedical applications and the potential future biomedical applications of marine-derived pectin.

**Keywords :** pectin, biomedical application, hydrogel, nanofiber mat, nanoparticle

## Introduction

### *Polysaccharide*

Carbohydrate are polymeric biomolecules found in living organism that serve as important energy sources. They also play significant structural roles as cellulose. A carbohydrate is a biomolecule composed of carbon (C), hydrogen (H) and oxygen (O) atoms, usually with a hydrogen – oxygen atom ratio of 2:1 (as in water); in other words, with the empirical formula $C_m(H_2O)_n$ (where m may be different from n). The most important carbohydrates in biochemistry are known as saccharides, a term derived from the Latin word for sugar (saccharum). Furthermore, many polysaccharides contain reactive functional groups such as amino, hydroxyl and carboxyl moieties. Because of their natural digestion and degradation in the human body, polysaccharide-based biodegradable matrices are gaining in-

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terest [1]. Polysaccharides are carbohydrate units comprised of several monosaccharides linked together by a glycosidic bond and arranged in long chains. They are also polymeric biomolecules found in living organisms and important sources of energy. They are also importantly structural roles such as cellulose, and have stated that their effects are structural dependent.

***Pectin***

Pectin (PT) is natural polysaccharide and biopolymer which was first was isolated in 1825 by Henri Braconnot. PT primarily serves as a structural component of plant tissue's primary cell wall. PT is a substance that binds cells and cells, as well as exists with cellulose and hemi-cellulose in cell membrane or between cells and cells. Hence, citrus fruits, apple, pear, and other fruits are used to extract and occupy PT. PT is more extracted in the peel and around the pulp than in the pulp itself. Types of PT contained in the fruit are distinguished by degrees of fruit maturity. It comes in the form of proto-PT in the immature stage. As the fruit mature, proto-PT transforms into PT. The PT enzyme converts it to pectic acid if it becomes more mature. However, proto-PT can be transformed to PT by heating with water. As a result, it is preferable to extract PT when the fruits are fully matured. PT has been characterized and evaluated for toxicity by JECFA (The Joint FAO/WHO Expert Committee on Food Additives). PT, according to JECFA, is distinguished by standard analytical methods for experiment and commerce.

PT is derived from linear polysaccharides, such as chains containing hundreds to thousands of saccharide units with average molecular weights ranging from 50 kDa to 150 kDa. PT is a heteropolysaccharide that consists of three major building subunits, namely homogalacturonan (HG), rhamnogalacturonan-I (RG-I) and rhamnogalacturonan-II (RG-II) [2]. PT is primarily composed of D-galacturonic acid linked by α-1, 4-glycosidic linkage. PT can be further classified by ratio of esterified galacturonic acid groups called degree of esterification (DE).

PT that contain more than half of its carboxylate units as methyl esters referred to as high methyl (HM) ester. In HM-PT, methyl ester has a relatively high carboxyl group ratio. It is primarily used in canning and gelation, and it requires large amount of sugar and is very sensitive to acidity [3]. In addition, PT that has less than 50% of the carboxylate units as methyl esters, is usually referred to as low methyl (LM) ester (Fig. 1). In general, low ester PT is obtained by slightly acidifying or alkalizing high ester PT. It shows less sensitivity toward acidity and requires $Ca^{2+}$ ions to form gel [3]. Moreover, amidated PT is produced through an alkaline process using ammonia to form high ester PT. In this process, some of the remaining carboxylic acid groups are converted to acid amides. The properties of the amidated PT can vary depending on the ratio of ester to amide unit ratio and the degree of polymerization. Commercial PT is usually combined with sugar for standardization, and some types contain buffer salts to adjust pH or to match desired properties. Polygalacturonic acid is partially esterified with methyl groups, and the free acid group is neutralized partially or completely with sodium, potassium or ammonia ions. The ratio of esterified galacturonic acid groups to the total galacturonic acid group, known as degree of esterification (DE), has a significant effect on the properties of PT, particularly its solubility and gel formation. PT has been reported to have a variety of bioactive properties including anti-cancer, anti- inflammatory, anti-oxidant, anti-diabetic, anti-cholesterol, anti-tumoral, chemopreventive activities, and etc [3-8]. Many researchers are interested in investigating and using PT as a medicine product.

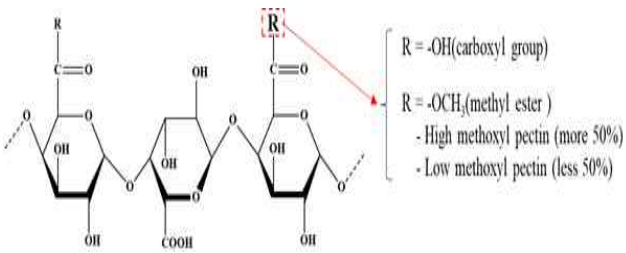


**Figure 1.** Structural formulation of PT.

***Preparation of pectin***

PT typically contribute to approximately 30% of the primary cell wall in fruits such as apple, and citrus [9]. Several techniques for extracting PT from natural product are well known, including those which use hot water, enzyme, microwave, ultrasound, and so on. Commercial extraction methods are commonly treated at high temperature with enzyme. The hot traditional method for obtaining polysaccharide is hot water extraction. Hot water extraction is performed in boiling water at 100°C [10]. The main disadvantage of using hot water extraction is the rupture of PT chains due to the prolonged extraction period [9]. The Enzyme-based extraction is based on the inherent ability of enzyme's to catalyze reactions with exquisite specificity, regioselectivity and the ability to function in aqueous solution under mild processing conditions [11]. However, when compared to the natural state of PT, the chemical structure of PT changed significantly during this phase with various extraction process. Hence, continuous efforts are being made to extract PT using "green" technology principles. [12].

***Marine pectin***

Due to the high availability of PT, researchers have recently investigated the composition of PT from marine organisms. Carbohydrates content in the algae ranges from 10-50 % in microalgae and 40-65% in macro-algae [13, 14]. Kyoung-Ah Lee et al reported that they investigated the composition of PT and the anti-oxidant activities of 5 species of micro-algae (*Spirulina maxima*, *Leptolyngbya sp*, *Tetraselmis sp*, *Dunaliella sp*, and *Chlorella sp*) and 9 species of macro-algae (*Saccharina japonica, Sargassum fulvellum, Undaria pinnatifida, Ecklonia cava, Gracilaria verrucosa, Gelidium amansii, Sargassum fusiforme, Ulva pertusa,* and *Sargassum horneri*) [15]. Furthermore, Edirisinghe, SL et al and Chandrarathna, H. P. S. U et al observed immunologic values of *Spirulina maxima* PT that have the potential to modulate gut microbial population, enhance the expression of immune related genes, and boost gut morphology in zebrafish larvae [16, 17]. Biological values of PT from *Spirulina* maxima for wound healing have also been recorded by Edirisinghe, S. L et al and Rajapaksha, Dinusha C et al [18, 19] Similarly, DS Domozych et al explain that *Penium margaritaceum* cells, green alga, has PT metabolism in the cell wall [20]. EDER et al. discovered PT-like carbohydrates in the cell wall and mucilage of the green alga *Netrium digitus* [21]. As previously stated, many researchers extract PT from marine species and investigate its efficacy, but research on the efficacy and value of PT is still insufficient.

## Biomedical application

Recent biomedical sciences advances are marked by an increasing number of papers and patents that maintain communication between clinicians and scientists. Advances in basic biomedical science have led to revision of theories of atherosclerosis, oncogenesis and aging, as well as a better understanding of basics of genetic, metabolic and inflammatory changes in human body [22]. Biomedical engineering is the integration of the various field of study mainly biological and engineering sciences. It has generally design concepts for the healthcare purpose. By developing advanced material and technologies, biomedical engineering seeks to enhance the people's quality of life. As an example, drug delivery agents, wound dressing, tissue engineering, and anti-bacterials are examples of biomedical engineering applications [23]. The most recent biomedical research advances are important emerging trends that hold a great promise in wound-healing management products [24]. Many researchers have worked on developing drug delivery system that assist in the effective delivery of the right amount of drugs at the right time into the wound in order to promote wound healing. Moreover, they have made efforts to fabricate barrier protecting wound site as well as scaffold for tissue growth [25]. Biomedical engineering applications could be typically divided with hydrogels, nanofiber mats, and nanoparticles.

**Table 1.** Summary of pectin based biomedical application

| Application | Material composition | Type of pectin | Source | Cross-link | Refs. |
|---|---|---|---|---|---|
| Hydrogel | Only pectin | LM | Citrus | $CaCl_2$ | [26] |
| | | - | Mandarin orange | $CaCl_2$ | [27] |
| | | LM | Citrus | $CaCl_2$ | [28] |
| | | LM | Apple | $CaCl_2$ | [29] |
| | | LM | Citrus | $CaCl_2$ | [30] |
| | | LM | Apple | $CaCl_2$ | [31] |
| | Collagen | HM | - | Calcium acetate | [32] |
| | Collagen, Gelatin | - | Citrus | Tyramine, EDC-NHS | [33] |
| | Gelatin | HM, oxidation | - | - | [34] |
| | Chitosan | - | - | Schiff reaction | [35] |
| | | Oxidation | Citrus | - | [36] |
| | | LM, oxidation | Citrus | - | [37] |
| | | HM, LM, oxidation | Citrus | - | [38] |
| | | Oxidation | Citrus | - | [39] |
| | | LM, oxidation | Citrus | - | [40] |
| | | Oxidation | Apple | - | [41] |
| | Alginate | - | - | $CaCl_2$ | [42] |
| | | LM | Citrus | $CaCl_2$ | [43] |
| | Cellulose | - | - | 1-Allyl-3-methylimidazolium chloride | [44] |
| | | HM | Citrus | Hydrogen bond | [45] |
| | | HM, LM | Citrus | $CaCl_2$ | [46] |
| | Gum | LM | Citrus | $CaCl_2$ | [47] |
| | | LM, oxidation | - | - | [48] |
| | Soy protein | -- | - | Laccase | [49] |
| | Fibroin | LM, oxidation | - | - | [50] |
| | Starch | LM | - | $CaCl_2$ | [51] |
| | Polyvinyl alcohol | - | - | Hydrogen bond | [52] |
| | Graphene | - | - | $MgCO_3$, $CaCO_3$ | [53] |
| Nanoparticle | Only pectin | HM | Citrus | $BaCl_2$ | [54] |
| | | HM, LM | Citrus | $MgCl_2$ | [55] |
| | | HM, LM | Banana | - | [56] |
| | Zein | HM | Citrus | - | [57] |
| | | - | Ivy gourd | - | [58] |
| | | HM | Citrus | - | [59] |
| | | HM | Apple | - | [60] |
| | | - | Citrus | - | [61] |
| | | - | Citrus | - | [62] |
| | | - | Citrus | - | [63] |
| | Gold | - | - | - | [64] |
| | | - | - | - | [65] |
| | Silver | LM | - | - | [66] |
| | | - | Apple | - | [67] |
| | Chitosan | - | - | - | [68] |
| | | LM | Citrus | $CaCl_2$ | [69] |
| | | HM, LM | Citrus | - | [70] |
| Nanofiber | Poly ethylene oxide | - | Citrus | - | [71] |
| | | HM, oxidation | Apple | - | [72] |
| | | LM | - | - | [73] |
| | | LM | - | - | [74] |
| | | HM | Citrus | - | [75] |
| | polyvinylidene fludene fluoride | - | Apple | - | [76] |
| | polyvinylalcohol, polyvinylpyrrolidone | - | - | - | [77] |
| | Polyhydroxybutyrate | - | Apple | - | [78] |
| | polyvinyl alcohol | - | Citrus | - | [79] |

## Hydrogel

Gels are very highly utilized materials that can be found all around us. The majority of gels are composed of polymers or colloids. They are filled with fluid. Gels have a higher elastic modulus (G') than a lower loss modulus (G"). As a result of that, though gels are soft, they have solid characteristics. Therefore, the term hydrogel is commonly used to describe hydrophilic gels [80]. Hydrogel is simply gel to interact with water and not to dissolve easily due to crosslinking forms as a chain network. Networks of hydrogel consist of hydrophilic biopolymers like proteins, polysaccharides, as well as synthetic polymer like polyvinyl alcohol. The majority of hydrogels are commonly formed by covalent interactions in these networks. Based on them, Natural and synthetic hydrogels are the two main types[81].

Natural hydrogels have been studied for a long time and have focused on the use of the biomaterials such as protein or polysaccharides [82]. Natural hydrogels are a common optimal for tissue engineering application since they are structurally similar to body components and have a high biocompatibility with cell and tissue [83]. They have also adaptable synthesis methods, low immunogenicity, and high water content. Hence, natural hydrogels have gained popularity among researchers due to their numerous benefits. Natural polymers that are frequently used include hyaluronic acid, chitosan, cellulose, alginate, gelatin and collagen.

Synthetic hydrogels offer many advantages, including precise control of chemical, mechanical, and physical properties as well as ability to design features that are easily manipulated for intended applications [84, 85]. Synthetic hydrogels were easily polymerized and customized in the laboratory scale. As a result, synthetic hydrogels can be tailored to specific applications by fine-tuning their mesh size, polymer length, water content, mechanical and chemical properties, etc.

Hydrogels fabricated by natural and synthetic polymer can also be modified to tolerate the variation in environmental conditions such as pH, temperature, salt, solute, electric current, and etc. As a result, they can be conveniently fabricated and used as suitable types in various e environments [86, 87]. Hence, they are collectively referred to as "smart" (or "intelligent") hydrogels [88]. Due to the extreme benefits listed above, hydrogels are often used in the biomedical applications such as tissue engineering, regenerative medicines, drug delivery systems, biosensor, wound dressing, diagnostics and isolation of biomolecules or cells and barrier materials to regulate biological adhesions [89]. Biological and biomedical application considers various physiological factors such as pH, enzymes, temperature, toxicity and biocompatibility and various physical characteristics of the applied tissue such as bone, dental, skin and tendon. Therefore, numerous amount of researchers attempted to fabricate hydrogels from a mixed range of biocompatible resource, including natural biomaterials like collagen, PT, alginate, hyaluronic acid and chitosan as well as synthetic biomaterials such as polyvinyl alcohol (PVA), polyethylene glycol (PEG) and polycaprolactone (PCL). Aside from biology, hydrogels have been used in various disciplines such as hygienic products, agriculture, sealing, coal dewatering, artificial snow, food additives and pharmaceuticals. According to Agaba et al, the moisture retention of a specific soil due to hydrogel is essential to the establishment of a plantation forest, as water regulate soil properties such as aeration, temperature and nutrient transport, water uptake and transformation, all of which affect plant growth [90]. Furthermore, hydrogels have been used as a control agent for applied fertilizer release in agricultural land against extremely porous soil, heavy rain, and other causes. [91]. In addition, amongst the most promising applications of hydrogels in food industry may be eco-friendly packaging solution that use biopolymer with ecological properties. They also provide antibacterial, antioxidant and nano-additives properties, Result of that, number of research groups and companies are designing eco-friendly and advantageous hydrogel based packaging solutions. [91].

***Pectin based hydrogel***

PT can be gelated using calcium chloride ($CaCl_2$), resulting in calcium pectinate hydrogels. Producing PT hydrogel is a simple, low-cost process in general. To prepare PT solution PT and deionized water were mixed and mechanically stirred for 24 h and subsequently, calcium chloride was added dropwise to the mixture and stored at room temperature for 1 h. For PT precipitation, methanol and 0.1 mol NaOH solution were added to the reaction mixture. The resultant hydrogels were washed three times with distilled water [28, 29, 31]. Some researchers have added glycerol, which has having non-toxic and viscous properties. Glycerol is used as a cross-linking agent for xanthan gelation in waterless or near-waterless environment, where its hydroxyl groups of glycerol can react with functional groups of xanthan [92]. Glycerol was added to the PT solution, which was then stirred for 2 h. Finally, the mixture was added to $CaCl_2$ solution to form a crosslinked hydrogel [26, 27, 30].

***Collagen/pectin based hydrogel***

Collagen is the most abundant protein in the extracellular matrix (ECM) and serves as a scaffolding in tissue. Type I, II and III of main types of collagen are found in connective tissue and account for 90% of all collagen in the body. The rigid, triple-stranded helical structure of collagen is its defining feature [93]. Collage has been used in various tissue engineering applications due to its admirable biological and functional properties [94]. GOEL, Himansh, et al has reported PT /collagen hydrogel for tissue regeneration application where they have initially 5 % (w/v) collagen and PT solutions were prepared in 10 mM Trizma buffer at pH 8.0 with calcium acetate solution. Gel formation was showed while addition of calcium acetate solution dropwise to the collagen/ PT solution and result showed with appropriate characteristics for the use of tissue engineering applications [32].

Gelatin is produced by the partial hydrolysis of collagen and is now widely used in the food, photographic, biomedical, medicinal and pharmaceutical industries [95]. Ahmadian et al fabricated PT /gelatin or collagen hydrogel with Tyramine using EDC-NHS. 10 g/L PT and 7 g/L PT /3 g/L gelatin powders were dissolved in distilled water for 1 hour at 40 ºC to yield PT and PT /gelatin solutions. 0.3 g tyramine, 0.1 g EDC, and 0.1 g NHS were overlaid to PT /gelatin solution dissolved distilled water for 24 hours. After 24 hours, the hydrogels were washed with 90% ethanol. Then, the hydrogel were formed by mixing 0.35 U/mL HRP and 0.1 mL $H_2O_2$ (0.1 mM) per mL of gel [33]. NEJATI, Sara, et al developed a PT/gelatin grafted polypyrrole hydrogel for tissue engineering application. Pyrrole was initially added to 100 mL gelatin solution (1 mg/mL) (gelatin grafted polypyrrole and oxidized PT were separately dissolved in PBS at the concentration of 8% and mixed at 37°C) and stirred for 30 min, and 17 mL $FeCl_3$ aqueous solution (0.2 M) was added gently and subjected to 24 h stirring at 4°C under nitrogen atmosphere. For hydrogel preparation, gelatin grafted polypyrrole and oxidized PT were separately dissolved in PBS at the concentration of 8% and mixed at 37°C for hydrogel formation [34].

***Chitosan/pectin based hydrogel***

Chitosan is widely known as the second most abundant polysaccharide in nature. It is a non-toxic, biocompatible, and biodegradable polymer derived from naturally occurring sources such as crustacean shells such as shellfish, shrimp, and crabs [96]. Chitosan is composed of randomly distributed β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine [97]. It is the semi-synthetically polymeric forms derived amino-polysaccharides [98]. Chitosan is suitable for the bio-applications due to its solubility in water and organic solvents [99].

GHORBANI, Marjan at el fabricated chitosan/PT hydrogel using oxidized and synthesized PT in $NaIO_4$ solution and ethylene glycol for 12 hours. The hydrogels were crosslinked by Schiff reaction of amino groups and aldehyde groups in chitosan and PT. As a result of their compacted network of smaller pore, they proposed that hydrogels could be useful for the application

in the field of tissue engineering[36]. Similarly, LI, De-qiang, et al also fabricated oxidized PT/chitosan hydrogel by Schiff reaction. Therefore, they claimed that the hydrogel was the excellent injectable, and self-healing, hydrogel with excellent magnetic, and high biocompatible properties in order to use as a potential candidate for drugs delivery [37].

NEUFELD, Lena et al and TENTOR, Fabio R., et al fabricated physically crosslinked PT/chitosan hydrogel. PT and chitosan were dissolved in hot 0.1M HCL solution (60°C) for 24 hours. After mixing solutions at 60°C for 1 h, mixture was transferred into mold to form hydrogels upon cooling to room temperature. Gelation temperature was demonstrated to decrease as PT concentrations were decreased using the tilting process. Since PT is completely negatively charged and chitosan is partially positively charged, electrostatic interactions can form between them, which caused the reduction of the mesh size of the hydrogel networks. Hence, they suggested that the thermoreversible PT/chitosan hydrogels have new potential to improve the life style of many patients by reducing the daily uptake of chronic medicines as drug carriers [40, 41].

***Alginate/pectin based hydrogel***

Alginate is an anionic polysaccharide with free hydroxyl and carboxyl groups found in the outer cell wall of brown algae. The linear, anionic polysaccharide consists of two kinds of 1,4-linked hexuronic acid residues, namely β-d-mannuronopyranosyl (M) and α-l-guluronopyranosyl (G) residues, arranged in blocks of repeating M residues (MM blocks), blocks of repeating G residues (GG blocks), and blocks of mixed M and G residues (MG-blocks) [100]. Alginate has attractive benefits for biomedical applications because of its biocompatible, PH sensitive, and high water absorbing properties [101]. Many researcher have studied continuously hydrogel based on alginate. For instance, ZHU, Yiming, et al and OH, Gun-Woo, et al fabricated $Ca^{2+}$ crosslinked PT/alginate hydrogel. They used interaction between ions and guluronate or galacturonate blocks in the presence of divalent cations which is known as an “egg-box” model. They suggested that higher PT content enhances mechanical properties, water absorption, and drug-releasing property of the fabricated hydrogels and which enhances its potential to use as a wound dressing hydrogel.

***Cellulose/pectin based hydrogel***

Cellulose is commonly known functionalizable biosynthetic polymer from plants, animals and bacteria [102]. Cellulose has a long linear chain like structure composed of (1,4) linked β-D glucopyranosyl units assembled into hierarchical structures of microfibrils with excellent strength and stiffness [103]. CHEN, Wancheng, et al fabricated PT/cellulose hydrogel using cellulose which was dissolved in ionic liquid 1-Allyl-3-methylimidazolium chloride for 5 h at 100°C and PT which was added and stirred for 3 h at 100°C. After the polymer solutions were mixed well and cooled to room temperature, hydrogels were soaked in an isopropanol solution and washed by deionized water to remove ionic liquid. The result suggested that the PT/cellulose hydrogel has outstanding thermal stability and a dense network structure [44]. In similar hydrogel, Komagataeibacter xylinus strain ATCC 53524 was cultivated in Hestrin and Schramm medium at pH 5 with a glucose concentration of 2% w/v adding 0.5% w/v PT and 12.5 mM $CaCl_2$ solutions. The sample was cultivated statically at 30°C for 96 h and washed 12.5 mM $CaCl_2$ solutions containing 0.02% $NaN_3$. They suggested the importance of the order of assembly of polysaccharides for cellulose composite hydrogels [46].

***Gum/pectin based hydrogel***

The term “gum” is used to describe a group of naturally occurring polysaccharides that is widespread in industrial applications due to their ability either to form gel or make viscous solution or stabilize emulsion systems [104]. Flaxseed gum, a main component of flaxseed (8% of seed mass), is a heteropolysaccharide that consisting of neutral and acidic components [105]. Gums are widely used in industries including adhesives,

biotechnology, biomedical, and cosmetics [106]. SYNYTSYA, Alla, et al fabricated PT and flaxseed gum hydrogel. 2% w/w PT and gum were dissolved in distilled water, and the pH value was justified to 7.4 by 0.2 mol solution of sodium hydroxide [47].

SLAVUTSKY and Aníbal Marcelo also developed a PT/brea gum hydrogel. Brea gum obtained for Cercidium praecox which has β-(1,4)-linked d-xylan backbone and containing some (1,2)-linkages substituted residues of d-xylose, l-arabinose and d-glucuronic acid. PT and brea gum solutions were prepared in distilled water at pH 4.2. After adjusting at pH 2.75 with HCl (1 N), the mixture was stirred for 3 min, centrifuged at 2000 rpm and storage at 5°C. They proposed that PT/brea gum hydrogel that can respond to pH changes and to drug releasing capability, may be valuable for medical and industrial applications [48].

***Soy protein/pectin based hydrogel***

Soybean contains approximately 40% protein, which protein is commonly used biocompatible polymer. It has a well-balanced amino acid composition and excellent gelling properties [107]. YAN, Wenjia, et al fabricated PT/soy protein hydrogel where soy protein and PT were mixed in distilled water and stirred for 4 h, mixture was then heated in 90°C for 30 min and stored at 4°C overnight for complete hydration, and subsequently, laccase was added in the mixture for gelation. Laccase is a promising biocatalyst for chemical synthesis [108]. They reported that the 14 U/g concentration of laccase caused a rapid cross-linking between ferulic acid in soy protein and tyrosine in PT [49].

***Fibroin/pectin based hydrogel***

Silk fibroin is biopolymer that is widely used in biomedical application due its attractive properties such as to elastic properties , biocompatibility, and biodegradability [109]. A team of researchers developed a hydrogel using oxidized PT and fibroin extracted from cocoon shell of silk worms. To prepare the hydrogel, oxidized PT and fibroin composite solutions were prepared in PBS and left at 37°C for ionic bonding gelation. They reported that polymer network was developed by interaction between aldehyde group in oxidized PT and amine group in fibroin, which gave stability to the hydrogel [50].

***Starch/pectin based hydrogel***

Starch is polymeric carbohydrate composed of glucose unit linked by glycosidic bonds which serves as the primary source of energy for humans. The starch is mainly consist of amylose and amylopectin consisting of chains of α-(1,4)-linked d-glucose residues [110]. DAFE, Alireza, et al fabricated PT/starch hydrogel. PT and starch were dissolved in distilled water and mixed at 70°C and subsequently, the mixture was added 0.2 M $CaCl_2$ to form ionic crosslinking between PT and starch itself and between PT and starch. They reported that PT/starch hydrogel was protected cell against the gastric tract and successfully released cell [51].

***PVA/pectin based hydrogel***

Polyvinyl alcohol (PVA) is water-soluble and hydrophilic synthetic polymer with various the numerous hydroxyl groups on the backbone. Particularly, PVA has the ability to bind monomer while remaining harmless and non-toxicity, low temperature crystallization ability, a high tensile strength property and high elongation property [111]. KIM, Jin and LEE, Chang-Moon used the freezing-thawing process to fabricate PT/PVA hydrogel. Following the preparation of a PVA and PT solution in distilled water, they were mixed and homogenized for 30 min. The homogenized solution was subjected three repeated freezing at −20°C for 18 h and thawing cycles at room temperature for 6 h. with clear results, they proposed that PT/PVA hydrogel has a potential as a therapeutic cover for burn or accident wounds [52].

***Graphene/pectin based hydrogel***

One of the most sophisticated carbon nanomaterials is graphene, which has a 2-dimensional single layer of carbon atoms in a hexagonal network and was dis-

covered in 2004. [112]. It is readily applicable to biomedical applications due to its unique mechanical and electro conductive property [113]. Due to those unique characteristics, numerous studies have been conducted resent past including the graphene hydrogel PT based graphene hydrogel developed by XU and his team. PT was dissolved in deionized water at 80° and stirred to formulate a homogenous solution. The crosslinking of PT was carried out by $Mg^{2+}$and $Ca^{2+}$ as ionic cross linkers, respectively through $MgCO_3$ and $CaCO_3$. Subsequently, Graphene oxide were carefully dispersed in the above solution, and then added trace amounts of HCl to adjust to pH 3.5 by which the carboxyl groups in PT were ionized, facilitating the ionic crosslinking of PT with divalent cations ($Mg^{2+}$,$Ca^{2+}$ions). After the complete ultrasound dispersal, the dispersion was sealed in a hydrothermal re-actor and maintained at 180°C for 12 min. Then the reactor was naturally cooled to room temperature and dialyzed against deionized water. They reported that the hydrogel was successfully fabricated by strong metal-carboxylate bonding between the PT, cations and graphene sheets [53].

## Nano-particle

Nanoscience is understanding to control of matter at nanoscale and recently focuses physics, chemistry, and biology [114]. Nano sized crystals are fabricated by quantum confinement effect depending on molecular and material character. Nanoparticle functionalities are controlled size-dependent [115]. The application of nanotechnology has been applied and developed for diagnostic or therapeutic purposes in medical fields [116]. Also, it has the potential of nanomedicine including single virus detection, DNA sequencing, gene therapy applications and the enablement of tissue engineering and manufacture of drug delivery system [117, 118]. Drug Delivery system are very attractive methods at controlled rate, slow delivery, targeted delivery [119]. Nanoparticles allow for the external delivery of substances that are constantly produced to restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate at the site of injury in body [120, 121].

### *Pectin based nanoparticle*

ERGIN, Ahmet Dogan, et al fabricated PT nanoparticle using ionic gelation method. After preparing the PT solution, the barium chloride solution and sodium bicarbonate solution were gradually added. Then the nanoparticles were obtained by stirring the solution at 600 rpm for 30 min at 25°C and subsequent centrifugation at 13 000 rpm, 10°C for 10 min. After three cycles, it is freeze-dried in the lyophilizator at −85°C. [54]. Similarly, JACOB, Eden Mariam, et al fabricated the nanoparticle by ionotropic gelation method using magnesium ($Mg^{2+}$) [55]. ARIAS, David, et al fabricated PT nanoparticle using SONICS VCX130 vibra-cell ultrasound probe. PT nanoparticles were prepared in a solution of ethanol: water in ratio 1:7 (v/v) as solvent by sonication. The mixture was sonicated with a SONICS VCX130 vibra-cell ultrasound probe, with a pulse function on 2 s and off 2 s, with 90% amplitude, 130 kW, for 5 min [56].

### *Zein/pectin based nanoparticle*

Zein contains the amino acid composition deficient in ionizable and polar, but it has the nanometer scale structure, biodegradability, and biocompatibility [122]. It is widely used in biomedical application since the cross-linking of zein molecules can be caused by chemicals [123]. JIANG, Yang, et al fabricated zein/PT nanoparticle. Initially, zein powder was dissolved in 80% aqueous ethanol solution and added into deionized water using ultrasound anti-solvent precipitation method to obtain the zein nanoparticles. Subsequently, zein nanoparticle and oil was added into PT solution. To prepare Pickering emulsions, disperse the mixture with a high-speed homogenizer at 14,000 rpm for 4 minutes. The results demonstrated that the zein/PT nanoparticle was successfully developed where PT led the excellent dispersibility and the potential slow-release ability compared zein-alone-nanoparticle [57]. Moreover, few more research teams also used similar method to fabricate

zein/PT nanoparticle, while they reported stability and release properties of few other drugs such as hyperoside, sesame oil, resveratrol, and caseinate [58-62]

***Gold/pectin based nanoparticle***

Gold nanostructures have proven and investigated to be a versatile platform for biomedical applications including diagnostics and sensing, imaging, and therapeutic techniques [124]. KHODASHENAS, Bahareh, et al and BORKER Shaivee fabricated PT/gold nanoparticle. Initially, chloroauric acid (HAuCl4) solution was boiled and added sodium citrate to obtain gold nanoparticle. Thereafter, PT solution which was obtained by dissolving PT in distilled water at 55°C was mixed with gold nanoparticle and stirred for 2 hours at room temperature. They reported that PT/gold nanoparticle was successfully fabricated by the absorption of the PT molecule on the surface of Au through physisorption with a charge transfer from the gold cluster to PT [64, 125].

***Silver/pectin based nanoparticle***

Silver nanostructures have been investigated as a potential material for biomedical application particularly in medical device coatings, antimicrobial agents, drug-delivery formulations, detection platforms, and diagnosis platforms [126]. HILEUSKAYA, Kseniya, et al fabricated PT/silver nanoparticle. AgNO3 aqueous solution and PT solution were mixed and stirred over 10 min, then pH was adjusted to 11 using NaOH. The synthesized PT/silver nanoparticles were purified by dialysis against distilled water. The results suggested that the PT/silver nanoparticle was successfully formed by ionic reaction between the carboxyl groups of PT and silver cations [66, 67].

***Chitosan/pectin based nanoparticle***

Chitosan/PT nanoparticle was easily fabricated by Pec/CS polyelectrolyte complex cross-linked with $Ca^{2+}$ [68]. The PT solution and chitosan solution of acetic acid were mixed in a certain ratio, pH of the mixture was adjusted to 10. WANG, Hui e al reported that electrostatic interactions between carboxyl groups on PT and amino groups on chitosan existed in PT-chitosan complex effecting the degree of esterification ratio and pH [70]. CHINNAIYAN, Santhosh Kumar et al reported that the electrostatic interactions and hydrogen bonding networks involving the two polysaccharides paved the way for the formation of chitosan-PT matrices [69].

## Nanofiber

Electrospinning is the most effective and advanced method for continuous nano- to micro-scale fiber. The fabricated nanofiber using this technique has interconnectivity, gas transport, large porosity, and large surface [127, 128]. Moreover, electrospinning is cost-effective and simple fabrication technique to control the architecture, biological property, and mechanical property using synthetic, natural, and composite materials [129]. Initial electrospinning technique was showed in 1934 and this technique was developed in nanotechnology. Continuously, many patents and paper increased remarkably since 1998 [130]. Electrospinning is a process of making fiber between nano-diameter to micro-diameter though high electric charge and voltage. Polymer solution change thin fibrous form by electrical stimulation. And then, there are several laboratory factors in order to change fibrous form. From among these, main laboratory factors are polymer properties, polymer solutions, flow rate of solution, voltage and capillary-collector distance [131]. High flow rate negatively affects fiber diameter and morphology due to lack of sufficient time for organic solvent evaporation. Also, capillary-collector distance is main factor for organic solvent evaporation and linear fiber diameter and changed according to type of organic solvent and power of voltage [132]. The core principle of electrospinning technique is formation of the cone jet created by electric potential between needle nozzle and substrate. Voltage causing electric stress is critical value factor to form nano-fiber due to conical shape known as “Taylor cone” formation [133].

***PEO/pectin based nanofiber***

PEO is widely used in controlled release system and biomedical application due to hydrophilic, non-toxic, insensitivity to the pH, high water solubility, and rapid hydration [134]. KIADEH, Shahrzad Zirak Hassan, et al investigated PT / PEO nanofiber mats with encapsulated folic acid in Zn-based metal-organic structure for tissue engineering application. To optimize architectural morphology of the nano fiber mats and mechanical properties, they used citrus PT and 1000, 2000, and 4000 kDa PEO composite. Composite mixtures with 4 wt% PT solutions and 4 wt% PEO solutions in 2% acetic acid and 1 wt% Triton X-100 were stirred for 6 h and stored overnight before the use for electrospinning. Nanofiber mats were then fabricated under the high voltage (17 – 20 kV) providing 18cm distance between syringe needle tip and the drum collector using 20-gauge stainless steel needle [71].

SHI, Xiaoqi, et al studied gelatin crosslinked PT nanofiber mat fabricated using PEO. Initially, oxidated PT (OP) was made by reacting with $NaIO_4$ solution for 16 h in darkness and then the resulted solutions were dialyzed against water and freeze-dried. Thereafter, OP and PEO (80:20) in 1% Triton X-100 and 5% DMSO was prepared and subjected to the high voltage (12kV) and electospuned and collected the nanofibrous mate to the drum collector kept at 14 cm from the using the needle with the 0.6 mL/h flow rate at 25 % humid environment. Thereafter they have used gelatin (5mg/mL in 70% EtOH) for the cross-linking of fabricated nano fiber mats and cross-linked under 37°C for 24 h. After cross-linking, the nanofiber mats were washed using ethanol and chloroform at 37°C to remove unreacted gelatin. They suggested that the gelatin-crosslinked PT nanofiber mats could potentially use for the regeneration of soft tissues due to their moderate mechanical strength, good water resistance, cell affinity, and excellent cytocompatibility [72].

Akinalan Balik, and his team also fabricated the nano fibers mat from PT and PEO. In order to fabricate nanofiber mats, they have first obtained the polymer solution, PT (low methyl esteri-fied [LM] amidated, DE = 27%, DA = 20%) in distilled water at 70°C and PEO (600, 1000, and 2000 kDa; 2 wt%) at room temperature were dissolved. PT and PEO solutions were then mixed at equal volume and stirred at room temperature overnight. Resulted composite was electrospuned using the syringe pump with the flow rate of 0.2 mL/h, using 0.8 mm gauge needle under high voltage (18-22 kV) to the drum collector kept at 20 cm distance from the syringe needle. It was observed that only PEO solution did not form fiber-forming jet while PT solution generated discontinuous droplets instead of forming continuous jets. This finding implies that solution viscosity is not the only indication of jet formation ability of a polymer solution, since PEO solutions formed jets despite having very low viscosities, while PT solutions did not form even at higher viscosities. Moreover, they found that high molecular weight of PEO was important to form smooth nanofibers when it is used with PT solution because of the generated high zero shear, tip viscosities, and high elastic modulus values. As a result, they proposed that fabrication of nanofiber mats using PT and PEO could be achieved by blending PT with high molecular weight PEO [73].

MCCUNE, Devon, et al were investigated fabrication of PT/PEO nanofiber mats cross-linked oligachitosan with plurocin F-127. The solution preparation parameters studied include 4% PT and 4% PEO solution from 70:30 to 40:60, flow rate from 0.2 to 1.2 mL/h, and voltage from 10 to 25 kV. Moreover nanofiber mats using the mixtures were fabricated by 25-gauge stainless-steel needle and 20 cm distance between syringe needle tip and the drum. After soaking in 95% ethanol for 2 min, nanofiber mats were cross-linked with oligochitosan in a 150 mM calcium solution. They suggested that the oligochitosan cross-linking treatment on PT nanofibers is preferable for tissue engineering purposes due to take a positive surface charge of nanofibers [74].

LI, et al fabricated oxidized PT and adipic acid aihydrazide (ADH) nanofiber scaffolds for use of differentiation of mesenchymal stem cells. Oxidized PT (OP)

was prepared by reacting PT with $NaIO_4$ solution for 16 h in darkness, followed by dialyzed against distilled water and consequent freeze-dried. Thereafter, nanofiber mats were fabricated using the mixture of OP (2% w/w) and PEO (5% w/w) in 1% Triton X-100 and 5% DMSO using optimal electrospinning condition (voltage of 9 kV, flow rate of 0.6 mL/h, gauge 9 needle and 15 cm distance between syringe needle tip to the drum at 30°C temperature and 30% humidity). OP of fabricated nanofiber mats were cross-linked with ADH solution (50mM in 80% EtOH) for 24 hours at 37°C. 5 mg OCP nanofibers were placed into (5 mL) ADH solutions shaken at 100 rpm for 8 hours. After the cross-linking reaction, the nanofiber mats were washed in ethanol and chloroform at 37°C to remove PEO and the unreacted ADH [75].

***PVDF/pectin based nanofiber***

HAMZAH, et al fabricated polyvinylidene fluoride (PVDF)/PT nanofiber mats containing benzalkonium chloride (BAC) as a drug. After preparing mixture of 10% (w/v) PVDF solution in dimethylformamide (DMF) and PT solution (1, 2, and 3 wt% in acetic acid), nanofiber mats were fabricated at room temperature using high voltage of 15 kV at flow rate of 1.5 mL/h while keeping10cm distance between syringe needle tip and the drum collector using a size 0.7 mm needle. The results proposed that the swelling and release behavior, and water contact angle of the nanofibrous has direct correlation to the percentage of PT incorporated in the composite polymer solution [76].

***PVA/PVP/pectin based nanofiber***

ALIPOUR, Reza, et al were investigated fabrication of PVA/polyvinylpyrrolidone (PVP)/PT/Mafenide acetate (MF) nanofiber mats containing Ag nanoparticles. After preparing 10% PVA solution, 5% PVP solution, 5% PT solution, and 20% MF solution, nanofiber mats using the mixtures of different concentrations were fabricated by voltage of 12-15 kV, flow rate of 0.6-0.7 mL/h, 9-gauge stainless-steel needle and 10-12 cm distance between syringe needle tip and the drum at 30°C temperature. PVA/PVP/PEC/MF nanofiber mats containing 0.2, 0.5, and 0.7 wt% were resulted to reduce the hydrogen bong and deteriorate of mechanical property by increasing the Ag content. But they confirmed that the MF loading into nanofibers has no effect on $Ag^+$ release behavior and the nanofiber mats were released Ag successfully for wound healing [77].

***PHB/pectin based nanofiber***

CHAN, Siew Yin, et al were investigated fabrication of PT/Polyhydroxybutyrate (PHB) nanofibers for retinal tissue engineering. PT-PHB was synthesized by ring-opening polymerization using tin(II) 2-ethylhexanoate as a catalyst. The reaction mixture comprised PT, β-butyrolactone, and tin(II) 2-ethylhexanoate (1:5:0.05) under an inert nitrogen atmosphere at 100°C for 24 h. After the reaction, Chloroform was added and stirred overnight at 50°C. PT-PHB solution dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol was fabricated by using 22-gauge needle, flow rate 1 mL/h, voltage 10 kV, and 7.5 cm distance between syringe needle tip and the drum [78].

***PVA/pectin based nanofiber***

PATRA, N et al were investigated fabrication of PT/polyvinyl alcohol (PVA) nanofiber mats. After preparing mixture of 11 wt% PVA solution and 2 wt% PT, nanofiber mats using the mixtures were fabricated by voltage of 60 kV and 15cm distance between syringe needle tip and the drum [79].

## Conclusions

PT is one of extensively reported natural biopolymer formulations for biomedical application. PT has various advantages as formulation due to its hydrophilicity, easy of ionic bonding, and biodegradability. As the research and development continues in PT based biomedical application, we expect to see many innovative and exciting applications in near future. Oceans cover about 70% of the Earth's surface and offer a number of valuable resources, many of which are yet to be discovered. Compounds found in marine organisms

have been shown to have high biocompatibility and strong bioactivity. In particular, algae offer many bioactive components and has thus been subject to significant research efforts. Many researchers extracted biomaterial from marine organism and investigated its efficacy, yet insufficient investigations were found in contrast to the efficacy and value of PT. Therefore, intense investigations are needed to characterize and utilize marine PT in biomedical application.

## Acknowledgements

This work was supported by the Pukyong National University Research Fund 2019.

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