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Review

Potential Biomedical Applications of Modified Pectin as a Delivery System for Bioactive Substances

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Abstract: Pectin is a polysaccharide that has been recently gaining attention because it is renewable, inexpensive, biocompatible, degradable, non-toxic, non-polluting, and has mechanical integrity. The recent extraction techniques and modification to the structural property of pectin have led to the modified pectin whose chemical and surface functional groups yield galacturonic acid and galactose contents which are primarily responsible for its improved and better use in biomedical applications including drug delivery and thus producing high-value products. Major attention on modified pectin has been focused on the aspect of its bioactive functionalities that opposes cancer development. Nevertheless, modified pectin can be combined with a wide range of biopolymers with unique characteristics and activities which thus enhances its application in different areas. This has enabled the current applications of modified pectin through different approaches in addition to the prominent anti-cancer functional capabilities, which were reviewed. Furthermore, this paper highlights the potential of modified pectin as a delivery system of bioactive substances, its synergistic and prebiotic effects, gut microbiota effect and antiviral properties amongst other roles applicable in the biomedical and pharmaceutical industries.

Keywords: pectin; modification; biopolymer; bioactive substances; biomedical applications; delivery system

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1. Introduction

The recent revolution in the world of biopolymers has far-reaching implications for the biomedical, pharmaceuticals, food and agriculture industries. The increasing demand for new, safe and improved biopolymer products has anticipated that the international market for biopolymers will be expanded by over 22.7% reaching approximately $19 billion between 2021 and 2025. This is expected to reach $29.7 billion by 2026 [1,2]. Biopolymer has become very appealing with intriguing benefits for application especially when they have barrier properties to moisture and/or gases, are non-toxic, non-polluting, are renewable, inexpensive, biocompatible and have mechanical integrity. These properties make pectin a suitable biopolymer for the delivery of bioactive substances. This has led to many studies investigating pectin applications in food, biomedical and pharmaceuticals [1,3–7]. Furthermore, recent studies have focused on the extraction and modification of pectin [8,9] and hence its application for a variety of industrial products, which offers itself as a better and environmentally friendly alternative for agro-industrial in line with bio-economy.

Pectin, one of the most significant polysaccharides, has been employed extensively in the food and pharmaceutical industries for many years due to its positive effects on health and abilities to gel, thicken, and emulsify liquids [10–12]. Even though chemical structures are crucial, it has not yet been possible to fully define the chemical structure of pectin because it is a complex natural molecule. The biological activity and gelation behaviour of pectin are significantly impacted by the extraction circumstances, plant sources, fragmentation strategies, and the structural complexity of pectin. An alternative

strategy is to alter their structure using the appropriate substances or techniques [13]. Although, the primary functional groups in the pectin chain are hydroxyl, carboxyl, and methoxyl. Physical, chemical, or enzymatic changes can cause modification of the structure of pectin and affects the functionalities of the carboxyl groups. This modification can be used alone or in conjunction with other biopolymers changing the structure of pectin. Pectin's structural makeup which includes the chemical and surface functional groups are primarily responsible for its use in biomedicine and drug delivery [14–16].

Recently, research interest has focused on the potential role of modified pectin (MP) piqued by this material's high-added value and distinctive behaviour. More attention has been given to understanding the characterisation, behaviour and application of MP for a decade. There has been a success in obtaining patents for the production of bioactive MP; nonetheless, studies are still ongoing to link a unique molecular structure to certain functionalities of MP and specific health-promoting effects. Pectasol-C is one of the most widely studied and characterized patent MPs [17–22]. The majority of biomedical research on MP focuses on health benefits through the approach of how MP opposes galectin-3 (Gal-3) via the modulation of immune functions, prevention of cancer or cardiovascular diseases, immunotherapy, etc [17–19]. However, there are very few studies that explore the health benefits of MP's bioactive functionality through the approach of delivery of bioactive substances such as probiotics, polyphenols, antimicrobial cells, and vaccines; translating it to biomedical or pharmaceutical applications. Therefore, the primary objective of this review article is to highlight recent extraction and modification techniques employed in pectin and how this could improve the benefits and approach in the application of MP in the biomedical and/or pharmaceutical industries.

2. Structural Properties of Pectin

2.1. Gelling Components

The characteristics and effectiveness of pectin in diverse applications are determined by its chemical composition and structure. Pectin is known to be a complex water-soluble polysaccharide containing 1, 4-linked α-D-galacturonic acid (GalA) as the predominant residue with a part of carboxyl group structure which makes it an acidic polysaccharide [23]. The basic assemble structure of pectin consist of domains: (i) Homogalacturonan (HG) is a linear homopolymer of α-1,4-linked GalA known as the "smooth region" (gelling area) containing some carboxyl group that can be methyl-esterified as shown in Figure 1A. It is a plentiful and ubiquitous domain making up roughly 60–65% of the overall amount of pectin [24]; (ii) Rhamnogalacturonan I (RGI) regions are highly branched with side chains neutral sugars which have led to the name "hairy region". Although the GalA residues in RGI are not methyl-esterified, they might be O-acetyl-esterified. The most common process of modifying pectin involves efficient de-polymerization of the commercial pectin either by an enzymatic modification or an alkali treatment. This results in β-elimination which cleaves and de-esterifies the HG backbone to create oligomers of poly-GalA on the RGI regions. It may be necessary to perform additional processing to cleave specific neutral sugars, which will mostly eliminate any arabinose residues and release modified RGI [25,26]. This modification produces unique bioactivity properties in MP which creates a chance for the free carboxyl group [27]. The capacity of pectin to gel is one of its most crucial characteristics [28]. The acetyl- and methyl-esterification of HGs are mainly responsible for the gelling property of pectin [29]. The formation of the gel is aided by inter- and/or intrachain associations in which different hydroxyl groups and free carboxyl groups interact hydrophobically to form hydrogen bonds, and/or ionic interaction. Hydrogen connections between secondary hydroxyl groups and undissociated carboxyl groups; or interactions between methoxyl groups and water are two processes that could cause alignment of the molecular helices. The presence of a high concentration of H^+ limits the ability of free carboxyl groups to dissociate, which lessens the electrostatic attraction between the molecular chains. Additionally, the availability of many sugars may reduce the hydrated radius of pectin which can cause interchain interactions as opposed

to chain-solvent interactions [30]. It was reported that carboxyl groups in GalA units are not negatively charged and cannot bind to divalent calcium (Ca^{2+}). However, pectin with low methoxyl values was found to generate gels with high viscosity and hardness, which in turn affected the formation of the egg-box structure and the mechanical properties of the gel [30]. Although pectin has a branched chain structure, mono-sugars in branched chains can prevent the pectin from attaching to Ca^{2+}, which can cause pectin not to gel [31]. It is important to mention that this may only apply to the RGI and not necessarily be the HG region. Different models have been put forth that the pectin backbone is made up of (i) alternating HG and RGI domains [32] (ii) perpendicularly connected-HG strands and RGI domain [33] and (iii) a combination of (i) and (ii) [23,34]. The functional characteristics of the HG domain can be changed by biochemical modifications.

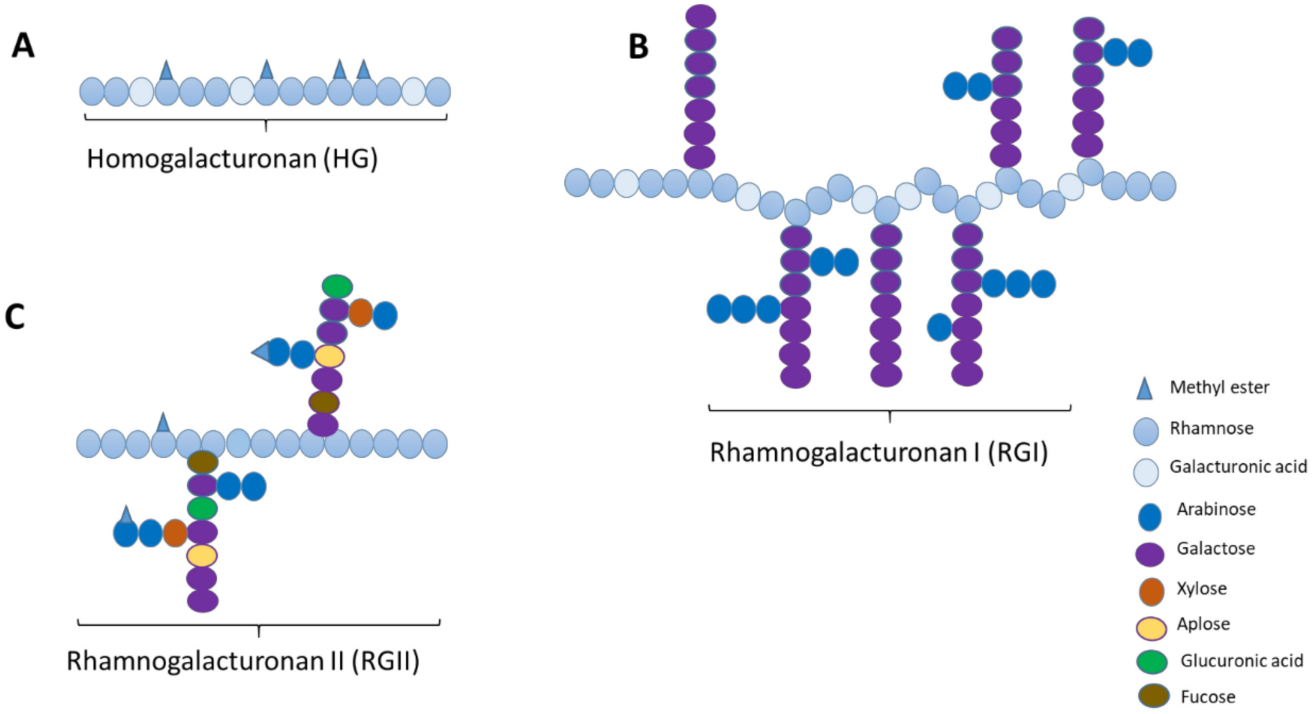

Figure 1. Simplified structures of modified pectin. (**A**) The Homogalacturonan (HG) "smooth region" is responsible for gelling (**B**) The Rhamnogalacturonan 1 (RGI) "hairy region" is responsible for non-gelling (**C**) Rhamnogalacturonan II (RGII) region [34].

2.2. Non-Gelling Components

The 'hairy' region of pectin (non-gelling area) is a substantial component characterized by branch points and composed of alternating α-(1-2)-L-rhamnose- α-(1-4)-D-GalA (1–20 residues) as shown in Figure 1B. This region is composed mostly of neutral sugar side chains mainly L-arabinose, D-galactose RGI, arabinans, galactans, arabinogalactans and other residues such as D-xylose and D-glucuronic acid [7,33] which can link to the Rhamnogalacturonan II (RGII) region as shown in Figure 1C. RGI regions may require further characterization even though the composition varies in different species of plant and the isolation technique matters. The RGI region (arabinans and galactans) adopts more flexibility which correlates more with the transition stages in the cell or/and tissue developments for instance, from cell division to cell elongation [23]. This hairy region which is more flexible is so important because galactan, arabinan and arabinogalactan side chains are located here and attached to the rhamnose residue. This relative flexibility and elasticity of the cell wall have been suggested to be likely due to the arabinans side chain attached to RGI [35]. Considering the arabinogalactans, there are two types attached to the rhamnose backbone residue; (i) the linear β-(1-4)-D-galactan which is most likely a structural weapon

with the great affinity of binding with the carbohydrate recognition domain responsible for cancer proliferation and metastasis and (ii) the branched β-(1-3,6)-D-galactan [34].

3. Degree of Esterification in Modified Pectin

Pectin can be classified as high methoxyl pectin (HMP) and low methoxyl pectin (LMP) depending on the structure of pectin, its gelling property, molecular size and degree of esterification. Esterification is simply put as when a GalA carboxyl group along the pectin chain has a large group of methyl attached to it while the degree of esterification (DE) is the ratio of GalA residues that has a methoxyl group attached to them to the free ones, in other words, the number of moles of methoxyl group in hundred moles of the residue of GalA. Different methods that can be applied to modify pectin include enzymatic and alkaline treatment. The HMP has a DE as high as 50% while LMP is less than 50% [36,37]. The DE $\geq$ 70% in industrial pectin can be reduced to $\geq$10% by the removal of the methoxyl group from the HMP to generate LMP and breaking down the molecular weight of industrial pectin into smaller uniform fragments of the smaller size of about 10,000–20,000 daltons [34,38].

The modified LMP can be developed into a delivery system by allowing the pectin to interact and react chemically with other polysaccharides, proteins, and cations molecules and thereafter homogenizing the bioactive substances by centrifugation or extrusion [39]. The LMP is frequently used to crosslink with cations to generate gels due to its versatility in the formation of gels over a wide pH range (2.0 to 6.0). LMP has fewer methyl esterified carboxyl groups (-$COOCH_3$) than non-esterified carboxyl groups (-COOH) as shown in Figure 2, therefore, it can cross-link more effectively with Ca^{2+} and polyelectrolytes [39]. An "egg-box"-like structure is created when the cations make ionic bonds with two carboxyl groups that are present on two different LMP chains. Contrarily, HMP's insufficient charge could also lessen its ability to interact ionically with cations [40]. Another study reported how the "egg-box" model of LMP gelation describes two nearby carboxyl groups from two distinct chains that generate ionic bonds through the development of calcium bridges [31]. LMP gels through ionic interaction in the presence of polyvalent ions such as calcium, and magnesium [28,41]. One advantage of LMP is that the strength of gelling increases as the DE value is reduced. This creates more chances for calcium to interact and bind with the carboxyl group, thus expanding the possibility of LMP binding as the concentration of calcium ions increases. Low temperature (10 °C) favours gel formation unlike high temperature and an increase in pH (less than 3) [42]. The interaction of two-fold helical chains forming an 'egg-box' structure is similarly envisaged in alginate and depicts the potential of pectin as an encapsulating agent (protecting core material from extrinsic factors).

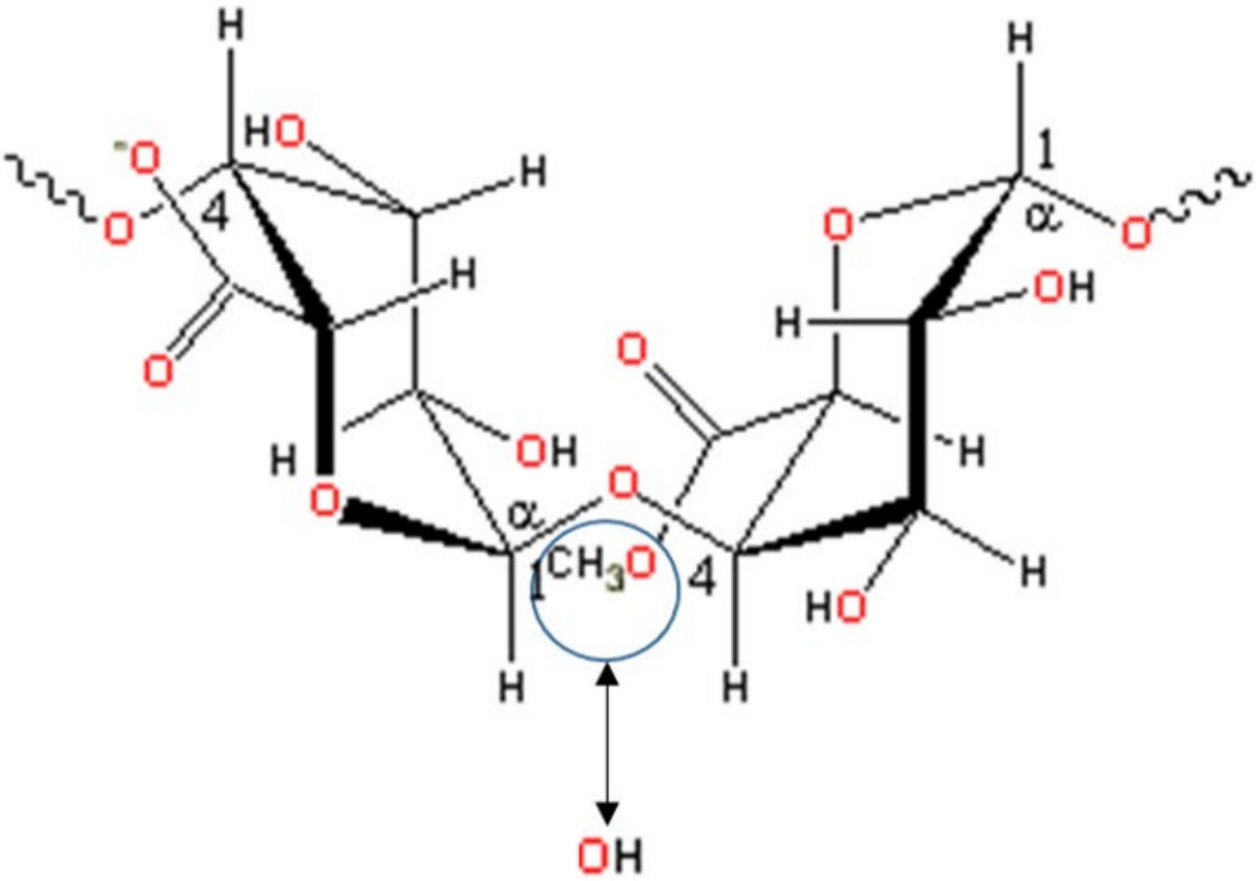

Figure 2. The schematic molecular unit structure of high methoxyl pectin (HMP) with –OCH_3 and low methoxyl pectin (LMP) when substituted with –OH Adapted from [43].

4. Recent Extraction Techniques of Modified Pectin

Recent studies have shown the separation of pectin from several by-products, including sugar beet pulp, lemon, sunflower head residues, passion fruit, and pomelo [44–47]. Nevertheless, apple and citrus fruits are the most popular sources of commercial pectin extraction. Pectin from various plant species demonstrated a variety of properties due to differences in chemical composition, molecular size, and DE values. By de-esterifying and depolymerizing, the traditional extraction techniques significantly damage the molecular structure of pectin. Technologies that are in development for extracting pectin have also been created to minimize harm to the chemical structure and composition while limiting environmental effects [48].

One of the conventional ways of extracting pectin from plant material/by-products such as citrus peel and apple pomace is acid extraction which involves the use of hot water (60–100 °C). Over time, the water becomes acidified with a mineral or organic acid [49]. Long extraction and high temperatures have the tendency of destroying the polymer structure and functionalities of the carboxyl groups in the pectin though. This may promote the quality yield of pectin, however, the quantity in terms of GalA, L-rhamnose, L-arabinose, D-xylose, D-Mannose, D-glucose and D-galactose, may be compromised [45]. Amongst many chemicals used for extraction include sulphuric and citric acids. Pectin of 21–40% DE extracted by superfine grinding, heating and enzymatic process formed gel at a concentration of 3% (w/v). However, such gelling property at low DE was not achieved in mild conditions at the same concentration [46]. In general, pectin extracted using sulphuric acid has a greater DE value than pectin extracted with citric acid. Under the same pH conditions, organic acid has a greater affinity for and contributes more protons to the pectin molecular chains than inorganic acid [50]. A study reported that alkaline

extraction produced the largest pectin production, and the matching GalA [51]. Therefore, to enhance the pectin extraction process and to boost the extraction yield, common emerging technologies such as ultrasound, microwaves and ohmic heating [52] were discussed.

4.1. Ultrasound

Ultrasound is a solid–liquid extraction technique that produces strong sonic energy (cavitation) phenomena by using high-frequency acoustic waves [53]. Mass transfer from the solid plant matrix to the liquid media and cellular disruption caused by cavitation are two characteristics of ultrasound [54]. Plant cell walls may cavitate as a result of ultrasonic treatment, which will alter the structure and morphology of carbohydrate polymers. This cavitation can lead to the release or formation of free radicals when there is a dissociation of water molecules, a change of cell structure and increases the yield of extraction [55]. GalA, which makes up the majority of pectin in its chemical structural analysis (65%), is the gold standard for purity [56]. The ultrasound technique can reduce the content level of GalA in the pectin to 71% [55]. A similar study comparing the GalA content in varieties of citrus reported a decreased level of GalA in tangerine which was within the range of 54–63% as a result of ultrasound [57]. However, another study demonstrated that ultrasound-assisted pectin has a low DE concentration (47–51%) and a high GalA content (75–90%) when exposed to NaOH and HCl [58]. A high yield of pectin extraction by ultrasound may be dependent on the pH condition [59]. Nevertheless, an increased power density of the ultrasound may lead to a maximum yield of pectin extraction [60]. Sunflower head pectin extracted using ultrasound was rich in low-esterified GalA content and long side branches of galactan, arabinogalactan, and arabinan [46]. This suggests that the difference in varieties of citrus or the source of pectin could determine the level of GalA obtained in ultrasound-assisted pectin.

4.2. Ohmic Heating

When alternating electrical current is delivered through a material with the primary goal of heating it due to the electrical resistance of that material, it produces a quick and consistent heating process known as ohmic heating or joule heating [61]. Ohmic heating creates a high-quality product with few modifications to the structural, nutritive, or organoleptic features due to an additional non-thermal action caused by the electrical field. Ohmic heating is also a more environmentally friendly technique that has drawn a lot of interest because of its advantageous qualities [62]. The optimization of pectin extraction from orange juice waste assisted by ohmic heating yielded the highest pectin at the optimum conditions of 67.18 $\pm$ 3.77% [63]. Although ohmic heating technology is an emerging technique with very little data report available. However, it may have a wide range of use in other biological processes, including food pasteurization, sterilization, evaporation, dehydration, fermentation, extraction, and blanching [63].

4.3. Microwave

Microwave is a heat dependent extraction technique that provide pressure and thermal effects as it uses electromagnetic waves that will interact with polar substances between 0.3 GHz and 300 GHz [64]. The increased molecular weight of pectin obtained via a microwave-assisted heating technique is advantageous due to its gelling capabilities. A microwave-assisted heating technique on potato pulp yielded a 59.75% higher pectin with high GalA content versus the heating method [65]. The use of a microwave technique might reduce the extraction time from 1.5 h to 4 min [66,67]. The combination of the microwave with the ultrasound method has the potential to improve the capacity of pectin to hold water, oil, cholesterol, and nitrite ions [68]. Comparatively, excellent water retention capacity and particle size characteristics were displayed by pectin extracted using a microwave-assisted technique. Additionally, pectin extracted using a conventional heating method and a microwave-assisted extraction method showed higher DE and GalA than pectin extracted using an ultrasound-assisted method while also having poor thermal stability. A

higher yield of GalA content (78.1%) and pectin (32.8%) were obtained when the surfactant technique was combined with microwave [69]. The extreme extraction circumstances of microwave- and ultrasound-assisted techniques considerably increase extraction efficiency while also influencing the physicochemical parameters [67]. The combination of microwave heating with any other techniques could improve binding abilities, however, microwave-assisted conditions should be carefully monitored because prolonged exposure can easily lead to excessive hydrolysis, resulting in increased pectin molecule breakage. In contrast, too little time can result in incomplete hydrolysis, resulting in lower yields [55].

4.4. Other Techniques

In addition to the technologies described above, other techniques such as such sub-critical water extraction, deep eutectic citric and pulse electric fields can suffice as shown in Table 1. Since microwave radiation is non-ionizing, it rarely weakens chemical bonds or modifies compounds' molecules as a result of electron migration [64]. Hence, the use of subcritical water extraction in a dynamic mode could optimize the operating condition (temperature and/or PH) to give a predicted pectin yield. The deep eutectic citric acid solvent was used to optimize the pH condition to obtain a relatively low yield of HMP [70]. In another study, the use of pulsed electric fields followed by microwave-assisted extraction enhanced the pectin yield and functional properties of pectin from jackfruit compared to the conventional method [71]. Furthermore, the ultrasound, microwave and ohmic heating were combined versus the conventional method using citric acid. The analysis performed showed that the ultrasound-microwave assisted pectin and the conventional one had high content in galactose, rhamnose, arabinose, glucose, and GalA with a high degree of methyl-esterification. Although both pectin possessed considerable antioxidant activities, the ultrasound-microwave assisted pectin had stronger antioxidant properties when compared to the conventional pectin [72].

Table 1. Emerging extraction technologies of modified pectin.

Source of Pectin	Mode of Extraction(s)	Outcome	DE (%)	Refs
Grapefruit	Ultrasound-microwave assisted	GalA and DE increase with an increase in microwave power and heating time	N/A	[55,56]
Citrus (Tangerine)	Ultrasound	Decreased content level of GalA to 71%	N/A	[57]
Finger citron pomace	Ultrasound	High GalA content (75–90%) when exposed to NaOH and HCl	47–51	[58]
Citrus	Ultrasound	The high yield of pectin extraction by ultrasound is dependent on the pH condition	N/A	[59]
Citrus (Orange)	Ultrasound	Increased power density leads to maximum yield of pectin extraction	LMP, HMP	[60]
Citrus (Orange)	Ohmic heating	The highest yield of pectin was ob-tained at the optimum conditions of 67.18 $\pm$ 3.77%.	$\geq$50	[63]
Pomelo peels	Ultrasound-microwave assisted	Higher GalA content was obtained from combined technique compared to single technique.	56.88	[64]
Potato pulp	Microwave	59.75% higher yield of pectin with high GalA content compared to the heating method.	N/A	[65]

Table 1. *Cont.*

Source of Pectin	Mode of Extraction(s)	Outcome	DE (%)	Refs
Beet pulp	Microwave	Reduced duration of extraction has effect on the mass and amount of pectin obtained.	N/A	[66]
Citrus (Lime)	Microwave and conventional heating	Energy-saving that speeds up the extraction process, a lower pectin yield and could be improved by longer irradiation time.	N/A	[67]
Grapefruit	Microwave and ultrasound	High holding capacity for water, oil, cholesterol adsorption, glucose and nitrite ions.	N/A	[68]
Citrus (Orange)	Surfactant and microwave-assisted	A higher yield of pectin (32.8%) and GalA content (78.1%).	69.8	[69]
Citrus (Pomelo)	Subcritical water	Extraction (pectin) yield and the rate was influenced by the temperature.	LMP	[70]
Citrus (Pomelo)	Deep Eutectic Solvents/Citric Acid	39.72% pectin yield was obtained and influenced by pH resulting in HMP	57.56	[70]
Jackfruit	Pulsed electric and microwave	Higher pectin yield was obtained compared to conventional extraction.	N/A	[71]
Jackfruit	Ultrasound-microwave-ohmic heating assisted	Combined techniques demonstrated significant antioxidant activity of pectin, however in some experiments, ultrasound microwave performed better than the conventional.	62–65	[72]

Abbreviations: LMP, Low methoxyl pectin; HMP, High methoxyl pectin; DE, Degree of esterification; N/A, Not Available.

5. Modification Techniques of Pectin

One of the novel characteristics that make pectin acceptable in the biomedical, pharmaceutical, and food industries is because of the successful technology to improve the functionalities of pectin by modifying its structural and biological capabilities. These modifications could be by a chemical which is alkaline and/or acid treatment (depolymerization, demethylesterification), ultrasound/ultrasonic irradiation, substitution (alkylation, amidation, and sulfation) and chain elongation (crosslinking) [48]. These techniques can be interlinked and form a combination of two or more methods. Based on the mode of operation, we can categorize the modification of pectin as (i) Chemical (ii) Enzymatic (iii) Irradiation methods as shown in Table 2. This modification improves not only the bioactivity but also the functionality of pectin [73]. It is important to note that achieving a specific target to modify pectin may depend on the choice or process of modification. In other words, one of the criteria for choosing how to modify pectin should depend on what function the modified pectin is expected to perform. With the understanding that the HG region is very crucial to the gelling property of pectin and for emulsion, gel stability and encapsulation, and the RGI region is more responsible for its anti-cancer and immune interaction effects, attention should focus on modifying the pectin to favour the desired properties.

Table 2. Mode of operation in pectin modification.

Source of Pectin	Modification	Outcome	Ref
Citrus	Chemical (Alkali and acidic hydrolytic)	Good room-temperature stability, improved water solubility, and pseudoplastic behaviour with lower viscosity	[74]
Commercial citrus	Chemical (TFA and H_2O_2)	HG: RGI ratio determines the anti-inflammatory activity and emulsion stability. H_2O_2 modified pectin promotes the selective growth of specific probiotics	[75]
Citrus	Chemical (NaOH and HCl)	The total charge density of pectin was raised and improved the interaction with the pea protein.	[75]
Citrus	Chemical (NaCl)	Reduced Mw and viscosity and increased MP density favour interfacial properties	[76]
Citrus	Chemical (glycine, glycine methyl ester, or glycylglycine)	The glycine methyl ester bound to the carboxyl groups of pectin molecules which led to the improved dissolution of pectin.	[77]
Citrus pulp	Enzymatic (Pectinmethylesterase)	The integrity of charged modify pectin hydrogel was maintained under simulated GI conditions showing good vehicles for colon-targeted delivery for probiotics with longer stability	[78]
Citrus	Enzymatic and chemical demethylesterification	The low methyl esterified low Mw pectin materials showed improved interfacial characteristics.	[79]
Citrus (Orange and lemon)	Enzymatic and endopolygalacturonase	Pectin showed complement activation in the classical pathway at 1.25 and 2.5 mg/mL stimulating the immune system.	[80]
Citrus	Enzymatic, and chemical demethylesterification	Due to its greater ability to chelate pro-oxidative metal ions (Fe^{2+}), low demethylesterified pectin displayed a higher antioxidant capacity than high demethylesterified pectin, methyl esters distribution pattern along the pectin chain only slightly affected the antioxidant capacity.	[81]
Apple	Ultrasonic irradiation	The primary structure could not be altered; however, the viscosity was high.	[82]
Citrus	Mono and dual frequency ultrasound irradiations	GalA content increased, but its intrinsic vis molecular weight and DE decreased.	[83]
Citrus and apple	Enzymatic and ultrasonic irradiation	Higher depolymerisation in pectin treated by ultrasound in the presence of nitric and citric acids than in water; high-methoxylated pectin has a degree of esterification > 50%, hence suitable as a gelling agent.	[84]
Citrus	Ultrasonication and Microfluidization	MP showed enhanced encapsulation capacity to shield cholecalciferol (vitamin D3) from UV deterioration	[85]
Citrus	Charge modification	Pectin could cover the entire surface and encase the probiotic cell in a hydrogel matrix, reducing its accessibility.	[86]
Commercial pectin	Cross-linking	LMP was found to be ~700 nm in size compared to high methoxylated pectin (~850 nm)	[28]
Citrus and Apple	Cross-linking	LMP–calcium gels showed rod-like junctions and point-like cross-links zones formed between surrounding chains and monocomplexes.	[87]

Abbreviations: TFA, Trifluoroacetic acid; H_2O_2, hydrogen peroxide; GalA, Galacturonic acid; MP, Modified pectin; LMP, Low methoxyl pectin.

5.1. Chemical Modification

Pectin can be modified through the effect of pH by alkaline (sodium hydroxide) and/or acid treatment which causes depolymerization ordemethylesterification. Citrus peel pectin was examined and modified under different pH conditions alkaline and/or acidic using Trifluoroacetic acid and hydrogen peroxide (H_2O_2). In a study utilizing H_2O_2 for modifying pectin, pH 4 was used to prepare HG-rich MP, while pH 10 was used to create MP with heavily branched RGI. The ratio of HG to RGI is the key distinction between the two. The high degree of structural branching of RGI, reducing the HG region increases the anti-inflammatory activity of MP while reducing the functionalities of the RGI region and/or increasing that of the HG region improves the emulsion stability of the MP [10]. When citrus pectin was modified by NaOH and HCl, the resulting MP was with reduced DE and raised the total charge density improving the interaction with the pea protein isolate. Although, H_2O_2-prepared MCP with low Mw (2.7–3.5 kDa) demonstrated better probiotic efficacy against *Bifidobacterium bifidum* ATCC 29,521 [75]. When modified with NaCl, the Mw and viscosity reduced while the MP density was increased. Lower Mw of the MCP favours interfacial properties though, it could probably prevent the emulsion from forming flocculation [76]. Citrus pectin was modified with glycine and by the use of intramolecular associations in polar organic solvents, the dissolution of pectin was improved [77]. The sequential alkali and acidic hydrolytic process employed to modify citrus pectin chemically presented a higher content level of RGI but with little effect on the DE. This indicates that chemical modification may affect the gel properties, dissolution in water and structural stability of the pectin [74].

5.2. Enzymatic Modification

An enzyme that is frequently used to modify pectin is called pectin methylesterase (PME). Commercial citrus pectin can be charged with PME to de-esterify HMP (72% DE) to the desired LMP (35% DE) which serves as a colon-targeted delivery system for probiotic, L. casei W8 [78]. Consequently, this reduces the zeta potential to −37 mV, and Mw from 177 to 143 kDa which significantly improved encapsulation efficiency (EE) and stability (99%) [78]. Among these, the change in zeta potential when HMP was de-esterified from 73% to 38% and bind with Ca^{2+} to encapsulate indomethacin, improved the binding ability to Ca^{2+} and considerably boosted the encapsulation efficiency (81%).This lowered the release of indomethacin compared to ordinary pectin of encapsulation efficiency (55–68%). This may be due to the modified pectin's lower zeta potential, which enhances the ionic contact between carboxyl and Ca^{2+} [40]. In some studies, the sequential combination of chemical and enzymatic modification showed improved functional properties of the modified pectin. For instance, after the enzymatic degradation of citrus pectin, the chemical approach was targeted to improve interfacial properties and the impact on emulsion stability [79]. In a study, it was demonstrated that endopolygalacturonase was used to modify citrus pectin showing complement activation in the classical pathway thus stimulating the immune system [80]. When the pectin was modified by chemical demethylesterification together with an enzymatic process, the antioxidant capacity was improved [81].

5.3. Ultrasound Irradiation

Under the circumstances of 20 kHz, ultrasound can allow for the production of MP with a low Mw (237 kDa). This may be connected to the fact that ultrasound irradiation may reduce the viscosity of pectin, promoting the interaction of hydroxyl groups with free radicals in the MP [82,83]. Although, a larger increase in the GalA content and a decrease in DE and Mw are the effects of mono-frequency ultrasound irradiation at 40 kHz. An increased ultrasonic intensity decreases the Mw [83]. Modification of citrus and apple pectin by power ultrasound in the presence of citric acids with enzymatic treatment causes high depolymerisation suitable as a gelling agent [84]. The antioxidant effects of pectin are connected to the RGI level in the pectin chain, which is increased by ultrasound [85]. Alternatively, charging modification pectin obtained from citrus could

encapsulate probiotic cell in a hydrogel matrix [86]. Also, a LMP–calcium matrix gel showed a point-like cross-links zones formed between surrounding chains and monocomplexes [87]. It is worth mentioning that ultrasound irradiation has been making leeway [88], however, the synergistic effect of combining it with other methods such as ultrasound-assisted enzymes can be used to speed up the process of modification, create simpler branches, and create shorter units. This dramatically lowers DE and protects the RGI area [89]. When EPG is combined with NaOH and HCl, pectin has a low DE (11%) and Mw (2.7 kDa) content [90]. Notably, whereas enzymatic MP formed soluble complexes with anthocyanins, ultrasound-modified pectin formed water-insoluble complexes with anthocyanins [91].

6. Applications of Modified Pectin in Biomedicals

6.1. MP Immune Interaction Effect

Low esterification, low molecular mass, and a high percentage of RGI domains are well-known properties of MP that yield an effective application in biomedical therapy as an adjuvant in oncological and immunological therapy. According to a recent study, using a more random and novel modification method produces pectin derivatives with lower molecular weight and new functional groups which result in new applications for pectin [84]. This MP has characteristics which may include: (i) the enrichment of de-esterified homogalacturonan oligomers and the depletion of type one arabinogalactans (AGI) and rhamnogalacturonan (RGI) in MP smaller than 3 kDa; (ii) the increase in AGI and decrease in RGI in MP between 10 and 30 kDa [92]; (iii) contains a higher proportion of galactoside residues than xylan and arabinan. The size and domain topologies of MP make it more bioactivities and a broader range of uses promoting its anti-cancer capabilities and behaviours by inhibiting migration, aggregation, and proliferation of cancer cells [92]. This modification or alteration in the structure of pectin creates a carboxyl group on the galactan to interact more with galactose-binding proteins which also increases the bioavailability of the free galactans [26]. This promotes the health-related benefits and therapeutic application of the MP as the case may be in some disease indications such as cancer, cardiovascular fibrosis, kidney fibrosis, renal injury, heart diseases, inflammations, viral infections and other immunologically related diseases [17,93].

The potential of MP to support the immune system, regulate oncogenes, and suppress tumour development, has led to its use as a nutraceutical or pharmaceutical product in cancer therapy [15]. The unique anti-inflammatory bioactivity of MP in humans being connected to the sugar-galactose-inhibiting cell signalling protein, Gal-3, is responsible for tumour cell proliferation and metastasis. This influences immune regulation and modifies intestinal homeostasis. Due to the clustering effect caused by Gal-3 binding to the cell surface, T cells are activated by a greater quantity of Gal-3 at this binding site, perhaps evading the immune surveillance system. More data has demonstrated how modified citrus pectin (MCP) affects immunomodulatory functions for the control of inflammatory cytokines. The anti-inflammatory cytokine IL-4 is increased by MCP in the spleen of treated Balb/c mice [94]. The pro-apoptotic protein Bim is expressed at a higher level as a result of MCP, which also inhibits modified apple pectin kinase activity and causes the cleavage of caspase-3 in PC3 and caspase-1.1 [22]. The immune system, T helper cells, pro-inflammatory cytokines (IL-17, IFN, and TNF levels), and anti-inflammatory cytokines (IL-4 and IL-10) can all be modulated by MP [94]. Infected cells can be destroyed by the immune response, which is mediated by macrophages, dendritic cells, and the differentiation of CD8+ T lymphocytes into cytotoxic T lymphocytes in the presence of probiotics [95]. Due to MCP's low level of methyl esterification, this specifically increases T cytotoxic and NK cell responses. The generation of nitrous oxide, the development of reactive oxygen species, and the activation of signalling pathways such as the Toll-like 4, type A hijacker receptor, NF-B, and glucan receptor are additional ways MP might accomplish this [96].

6.2. MP Micro- and/or Nano-Encapsulation and Delivery System

Encapsulation is a versatile technology that involves the entrapment of bioactive materials whose application ranges from cell therapy to drug delivery. Pectin can interact with other biological components through a variety of changes which can provide more durable delivery systems, such as emulsions, hydrogels, liposomes, and microcapsules. The incorporation of bioactive components that can deliver functional attributes beyond those of conventional active packaging is among the few basic categories of nanotechnology application [97]. Pectin is also highly biodegradable and biocompatible, which makes it a fantastic carrier for colonic medications and bioactive compounds [98]. HMPs are used in some applications as an encapsulating agent in drug administration because they have a larger molecular weight and poorer solubility in water. However, early release and coating degradation might happen when the pharmaceutical product is encapsulated with HMP. LMP has been utilized more frequently in this regard though [99]. Recent studies have cited the combination of MP with other natural polymers, such as chitosan, or bioactive compounds, such as curcumin and cysteine, to avoid early release, increase gel resistance, decrease water solubility, reduce erosion capacity, and generate new materials with specific properties required for drug delivery [100–102]. It was suggested that a chitosan/pectin composite membrane of various compositions fabricated with a freeze-gelation method could be an ideal technique for MP-based material encapsulation. Chitosan is a positively charged polysaccharide (polycation) incorporated with pectin to form composite material as the ionic interaction between the polycation and polyanion leads to the formation of a polyelectrolyte complex [103,104]. The diverse controllable biodegradation rate of the composite membrane makes it a useful disintegrant carrier of bioactive materials with pectin significantly improving the membrane properties which include hydrophilicity, tensile strength, and water uptake [105]. The gelation or cross-linking of pectin can be achieved due to the strong inter- or intra-molecular interactions formed between the Ca^{2+} and pectin carboxyl anions group. The abundance of the anions on pectin is ionically cross-linked by Ca^{2+} because the cations possibly bind with different groups of carboxyl [106,107]. These properties imply that blending MP with other polymers has a potential means of controlled release of encapsulated bioactive materials such as probiotic bacteria in the gastrointestinal tract (GIT). The applications of using MP as a delivery system of bioactive materials to the target site are very promising. However, it is imperative to understand that this approach may differ depending on the bioactive substances that are being encapsulated. In this review, we will look at the most common bioactive substances that have been employed in the biomedical such as probiotics, vaccine products, and polyphenols.

6.2.1. Probiotics

Probiotic meaning ‘’ for life” is defined as “live microorganisms that beneficially affect the host’s health by improving its microbial balance” [108]. The nutritive value and health benefits of probiotics have recently increased the demand for improving nutritional supplements and hence become important. Probiotics encapsulation has successfully prevented cells from the adverse environmental effect, and improved their survival during storage and processing, releasing them in their viable and metabolic active states in the intestine under specified conditions and extending their shelf life [109]. This encapsulation delivery system can be explored to the advantage of probiotics even though different probiotics encapsulation techniques tend to produce microparticles or microcapsules (ranging from 1 µm and 5 µm diameter). In the application of polysaccharides in the pharmaceutical industry, drugs are entrapped by coating with alginate, and chitosan microcapsule which enables the controlled release of the drug under specific simulated intestinal conditions [110]. Such effect has been noted in the pharmaceutical industry including probiotics [111]. Polysaccharides such as pectin are biodegraded by the colonic microflora possessing the ability of controlled release as they are used as a target delivery means of drugs. Pectin is not degradable at the upper GIT and is a low-cost polysaccharide that has been utilized as a biopolymer matrix for the release of small drugs for colon-specific delivery [112].

Previous studies of over a decade ago have been reporting the use of ordinary pectin combined with other bioactive substances. For instance, pectin particles coated with whey protein protected and improved the survival of *Lactobacillus* from a low pH of 1.2 when exposed to simulated gastric compared to free bacterial cells [113,114]. Similarly, another study showed that the blend of pectin with alginate into microcapsules improves the protection and survival of *L. casei* at low pH in a simulated gastrointestinal condition [115]. The encapsulation of *L. plantarum* in different blends of sodium alginate, pectin or chitosan coated-sodium alginate was tested under simulated gastrointestinal, refrigeration and in yoghurt conditions but viability was improved as the lowest loss of viability under refrigeration as compared to the free cells was seen in pectin; sodium alginate coated with chitosan; a mixture of 2% (*w*/*v*) sodium alginate + 2% (*w*/*v*) pectin accordingly [116]. From this study, it can be suggested that a blend of sodium alginate and pectin coated with chitosan may further improve and enhance the stability and survival of probiotics in yoghurt under refrigerated conditions. An optimal count of *L. casei* higher above the therapeutic requirement of 10^7 cfu/mL in yoghurt was obtained in a 2% pectin bead or 2 and 3% pectin combined with 0.5% alginate [117]. The incorporation of starch and other additives may help to improve the stability of the microsphere during storage [116,118].

However, the recent use of modified pectin has shown potential in terms of encapsulation capability, delivery efficacy, and integrity (Table 3). A recent study reported LMP H_2O_2-prepared MCP showed a good encapsulation property on the probiotic, *Bifidobacterium bifidum* ATCC 29521 [75]. LMP gels through ionic interaction in the presence of polyvalent ions such as calcium. One advantage of LMP is that the strength of gelling increases as the value of DE is reduced. This creates more chances for calcium to interact and bind with the carboxyl group thus expanding the possibility of LMP to bind as the concentration of calcium ions increases. Low temperature (10 °C) favours gel formation unlike high temperature and increase in pH (less than 3) [42]. In another study when the citrus pectin was de-esterified from 72% DE to 35%, the hydrogels' integrity was preserved under simulated GI circumstances when 99% of *L. casei* W8 was encapsulated in calcium ionotropic gelated block charged low methoxy pectin hydrogels and no *L. casei* W8 release was seen. Encapsulated *L. casei* microbial counts varied from 6.94–10.89 $\log_{10}$ cfu/g and were 1.23 $\log_{10}$ cfu/g higher than non-encapsulated *L. casei* W8. Using just charge-modified pectin as the encapsulating material, the hydrogel-encapsulated *L. casei* W8 demonstrated good colonic-targeted release capability [78]. The increased efficiency of charge-modified pectin is most likely owing to the creation of numerous, strong junction zones that trap lactic acid bacteria in multiple layers of a pectin gel network and inhibit simulated intestinal fluid diffusion [78]. It is important to mention that the degree of methoxylation for MP is critical for the efficiency of microencapsulation and beneficial for probiotics. Typically, HMP gel which esterifies at approximately 65% through hydrophobic interaction and hydrogen bonding requires an acidic medium (for electrostatic repulsion) and sugar (sucrose to reduce polymer-water interaction).

Table 3. Applications of (modified) pectin as a biopolymer matrix.

Biopolymer	Bioactive Substance	Model	Type of Encapsulation	References
Citrus pectin (modified)	*L. paracasei LPC-37, B. bifidum ATCC 29521*	Broth medium	Emulsification/freeze drying	[75]
Pectin methylesterase modified pectin;	*Lactobacillus casei W8*	SGI	calcium ionotropic gelation	[78]
Charge-modified citrus pectin	*L. paracasei subsp. paracasei L. casei W8*	Wistar rat	Iontropic gelation by extrusion	[86]
Alginate; modified pectin; Chitosan	*L. acidophilus*	SGI	Emulsification	[119,120]
Pectin/gelatine	Cysteine protease *(Clostridium difficile)*	Hamster and SGI	Cross-linking	[121]
Pectin/gelatine	Flagellin *(Clostridium difficile)*	Hamster and SGI	Cross-linking	[122–126]
Alginate-modified pectin-Chitosan	*L. acidophilus*	Balb/c Mice	Emulsification	[127,128]
Pectin-derived oligosaccharides	Galacto-and fructo-oligosaccharides	Influenza vaccinated mouse model	N/A	[129]
Pectin-like polysaccharides	Blueberry anthocyanin extract	SGI	Emulsification	[130]
Pectin Strawberry fibre	Phenolic compounds	SGI	N/A	[131]
Lysozyme and κ-carrageenan	Curcumin	SGI	Emulsification	[132]
Pectin and biopolymeric skimmed milk powder	Curcumin	Caco-2 cells	Dispersion and homogenization	[133]
Modified citrus pectin and chitosan	Curcumin	SGI	Extrusion	[134]
Pectin and lactoferrin	Curcumin	In vitro	N/A	[135]
Pectin and doxorubicin	Doxorubicin	SGI	Ionotropic gelation and extrusion	[136]
Polymeric nanocarrier–curcumin	Curcumin	Azoxymethane-induced rat model	Emulsification	[137]
Pectin/calcium	Curcumin	SGI	calcium ionotropic gelation	[138]
Pectin/calcium	Epigallocatechin gallate and curcumin	Bacterial cell/human cell	N/A	[139,140]

Abbreviation: SGI; Simulated gastrointestinal conditions.

The efficiency of the MCP-alginate coated chitosan containing *L. acidophilus* ATCC 4356 microbeads was significantly improved when tested in simulated GIT conditions. The exposure of the MCP-alginate-coated chitosan microbeads to 3 h of simulated GIT resulted in 82.7% survival of *L. acidophilus* ATCC 4356 [119] (as shown in Figure 3).

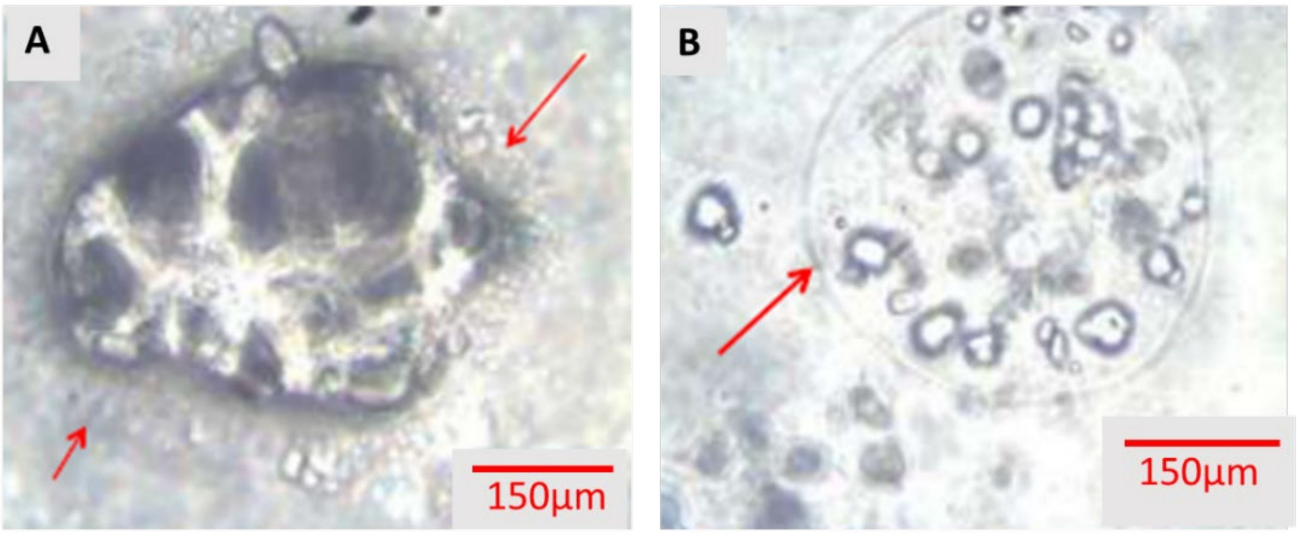

Figure 3. Light microscopic morphology of microbead encapsulation of *Lactobacillus acidophilus* ATCC 4356 probiotic by (**A**) modified citrus pectin alginate showing the chitosan coating effect (red arrow) and (**B**) sodium alginate particles produced by modified emulsification [119].

In an in vivo study, the MCP-alginate-coated chitosan microbeads significantly ($p < 0.05$) enhanced the viability of *L. acidophilus* ATCC 4356 compared to the sodium alginate-coated chitosan microbeads and free cells. An increase (10.2%) in the number of faecal lactobacilli from the colon tumour-bearing mice was noted after 28 days [119,120].

6.2.2. Vaccine Products

A study designed an oral vaccine against *Clostridium difficile* by encapsulating the virulent factor Cwp28, cysteine protease highly immunogenic in a patient with *C. difficile* infection in pectin beads [121]. Such novel vaccines encapsulated in a nanocarrier of MP can be developed for targeted specific site delivery. The encapsulation delivery system can be explored to the advantage of oral vaccine delivery. In another study, a colonic release vaccine for *C. difficile* that is administered orally contains FliC (flagellin) in pectin beads. Using simulated intestinal media, bead stability and FliC retention were demonstrated in vitro intestinal and colonic media, as well as the hamster model. The findings imply that oral immunisation with FliC-encapsulated pectin beads most likely triggered a protective immune response in the mucosa [122]. It was suggested that "nanoencapsulation of a designed bacterial material could be delivered to specific parts of the gastrointestinal tract where they interact with specific receptors or tissue by acting as de novo vaccines, capable of inducing immune responses" [123]. Studies have shown that colonization factors are the current targets of *C. difficile* vaccine development methods. While current clinical trials are using systemic vaccinations that target toxins, they have demonstrated efficacy in preventing *C. difficile* infection in animal models [124,125]. However, targeting colonization factors could stop *C. difficile* colonization, growth, and symptomatic infection, restricting the bacteria's ability to spread throughout the environment. Some potential vaccines that target colonization factors have produced encouraging outcomes [121,126].

Another approach to considering the beneficial application of MP is as an immune booster or adjuvant to a vaccine. Recently, the emergence of respiratory viral diseases such as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) due to mutation has caused amino acid changes in vaccine-targeted structural proteins. This, however, tends to question the host's long-term protection from infection after vaccination and/or the maintenance of a particular resistance to reinfection, hence the potential need for further booster shots. The inclusion of the administration of probiotics and MP in addition to vaccines suggests an adjuvant effect on the immune system and improves the immunological

protection of host cells against infection [127]. The initiation of MP and the adhesion of probiotic bacteria to specific receptors on the epithelial cell surface of the colon inhibit the extracellular matrix interactions [128]. The immune response emitted from the intestine due to the probiotic-MP adjuvant effect with a vaccine that is taken orally may increase butyrate, a colonocyte fuel which may prevent viral invasion or adhesion to the mucosal cell walls. In models of allergic asthma and murine influenza vaccination, MCP activates the Th1 T-helper immune response [129].

6.2.3. Polyphenols

Micro/nano-encapsulation protects the activity of polyphenols under gastrointestinal circumstances, allowing for their delivery to the target location [130]. Through encapsulation, polyphenols and pectin have covalent and non-covalent actions that can interact with gut bacteria [131]. The use of polyphenols is restricted due to their instability and low oral bioavailability, as well as by gastrointestinal digestion's chemical and enzymatic conditions that may alter their bioavailability [132]. Currently, chemotherapeutic alternatives include anticancer substances with plant origins, such as curcumin. These substances which are safe even at high concentrations come from natural sources and are thought to have comparatively fewer negative effects [133,134]. Curcumin, however, has low systemic bioavailability and is highly susceptible to metabolic activity, according to preclinical and clinical data from oral administration. This suggests that curcumin undergoes significant metabolic changes in the intestine and liver, which limit its systemic utility in the treatment of cancer [134]. Numerous delivery methods have been tried to increase curcumin's bioavailability to get over this restriction, including polymeric micelles, nano complexes, nanoemulsions, liposomes, conjugates, and lipid nanoparticles [135]. Drug trapping in polymeric drug carriers, such as hydrogels and nanoparticles, is one promising method of delivery [136]. Pectin stands out among the prospective curcumin nanocarriers because it successfully penetrates the gastrointestinal epithelium, allowing it to get around the digestive tract's metabolic constraints [134]. A study demonstrated an anticancer effect of nano polymeric curcumin in the colon of a typical animal model [137]. In Ca^{2+-} induced gel beads, Ca^{2+} and MCP produced a thick shell that significantly reduced the release rates of curcumin in simulated gastric conditions. In contrast, the pectinase activity in another simulated fluid system resulted in a weakening of the crosslink between pectin and $Ca^{2+,}$ allowing the release of curcumin from the gel beads [138].

As a result of the small size nature of nanoparticles, microscopy reveals that polymeric nano-carrier was easily placed within host bacteria [139] which suggests that polymeric nano-carrier curcumin capable of anticarcinogenic effect may be placed with host probiotic bacteria cells and entrapped with MP thereby enhancing the probiotic effect in the GIT of the consumers. Encapsulation in nanoemulsions could enhance the health benefits of curcumin and improve the stability and oral bioavailability of epigallocatechin gallate and curcumin [140].

6.3. Prebiotic Effect

Prebiotics are known to enhance probiotics' efficacy in terms of vitality, survival in the gastrointestinal tract, adhesion (colonization), and growth. The synergy between these two has generated a health-promoting effect. The most commonly used and widely accepted prebiotics are fructooligosaccharides (FOS) and inulin [141] but recently, a group of researchers found that pectin displayed a better prebiotic activity than inulin by enhancing the adhesion of *Lactobacillus rhamnosus* to the intestinal epithelial cells and decreasing the adhesion of *Salmonella typhimurium* (pathogenic bacteria) [142]. The approach of MP to probiotic and prebiotic interaction which invariably gives a synbiotic effect improves cell viability and protection during storage [143–145]. The concept of synbiotics can be defined as 'a mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and implantation of live microbial dietary supplements in the GIT, selectively stimulating the growth and/or activating the metabolism of one or more of health-promoting

bacteria, and thus improving host welfare' [117,146]. Prebiotics are nondigestible carbohydrates that, indirectly benefits the host, when consumed in substantial amount by selectively influencing the growth and survival of the specific genera of beneficial bacteria in the colon [147–149]. A food ingredient is classified as a prebiotic when it can resist acidity absorption of the GIT and hydrolysis of the human enzymes, the ability of the gut microbiome to ferment it, and selectively stimulate the growth and/or activity of the gut health-promoting bacteria [150,151]. Prebiotics prevent the binding of the pathogen to the intestine and increase the growth of beneficial bacterial. The most common prebiotics are inulin, fructooligosaccharides, and of recently pectin, because of their ability to resist the effect of gastric acid and pancreatic enzymes. Pectin exhibits prebiotic properties on different strains of probiotic microorganisms as there combination with some polymers such as alginate is effective in protecting *L. acidophilus* and *L. reuteri* during storage for a month at 4 °C [152,153]. Beneficial microbes may thrive in an environment enriched with specific nutrients which invariably can improve probiotic functionality through the modification of intestinal adhesion factors for instance the presence of certain carbohydrates such as inulin and pectin modulates the bacterial cell surface adhesion to intestinal cell models [154,155]. The influence of pectin on the bacterial adhesion of *L. rhamnosus* elucidates the potential gut health benefit of pectin.

A better understanding of the effects of MP starting from the release of the galactans, to the transit, digestion, colonic fermentation and circulation of the within the body would allow the optimization of MP as an alternative therapy [26]. This also implies that MP may need particular supplements to achieve maximum bioactivity [34]. In a study examining the effect of MCP and L. acidophilus ATCC 4356 on colon lactobacilli microbiota in healthy Balb/c mice the oral consumption of both the MCP and the probiotic causes a consistent increase in the faecal lactobacilli population [120]. This is indicative that MCP could have stimulated other colonic bacteria and not only the probiotic. The effect of MP could encourage the proliferation of lactobacillus species which is dependent on the composition and prebiotic index of the pectic fraction-arabinan and galactan [156], degree of methoxylation and selective fermentation of pectin [157]. Probiotics may feed on MP and produce secondary metabolites that inhibit the growth of non-probiotic microorganisms [48]. However, one of the key roles of the intestinal lactobacilli is to maintain the integrity of the epithelial mucosa of the intestine via the ability to catabolize complex polysaccharides into short-chain fatty acids (SCFAs- butyrate, lactic acids, acetic acid and propionate) which are major energy source to the epithelium cells of the colon [158]. MP could influence metabolism in the gut through colonic fermentation thus affecting intestinal bacteria [99]. Thus it is plausible to presume that the disintegration of MP by endogenous gut microbiota might have induced SFCAs, gases and butyrate for their survival. These SCFAs reduce the effect of bile in the intestine by initiating bile salt hydrolase which deconjugates bile acid [159]. Supplementation of lactobacillus with prebiotics could reduce bile acid conversion whose reabsorption into the gut may become co-carcinogenic [160]. The metabolic activity exhibited by *L. acidophilus* DSM 20079 in the presence of pectin and inulin to produce SCFAs most especially butyrate which is the preferred energy source for colonic epithelial cells can induce changes in gene expression and constitutes a target for improving their physiology to GIT-stress condition tolerance, selective stimulation of its growth and also affecting its subsequent expression of certain proteins [161,162].

The effects of non-encapsulated or charge-modified citrus pectin-encapsulated probiotic *L. paracasei subsp. paracasei L. casei* W8 on gut microbiota composition and metabolic profile was tested in Wistar rats fed with a high-fat diet. Pectin-encapsulated probiotics did not influence the benefit of probiotic administration. However, pectin encapsulation improved glucose tolerance, probably due to the prebiotic and/or synbiotic properties of the pectin utilised as encapsulation material [86]. *L. acidophilus* DSM 20079 was grown with inulin and/or pectin as a source of carbon evaluating the viability, growth, activity and composition of whole-cell protein as the probiotic strain is passed through the simulated intestinal condition. The data obtained was indicative, selectively stimulating the growth of *L. acidophilus* DSM 20079 compared to glucose, resistance to stress in simulated gastric conditions and subsequently positively affecting the expression of a protein which leads to the synthesis of some important healthy bio-compounds such as butyrate [161].

6.4. Gut Microbiota Effect

Recent research suggests that the structure of pectins, such as DE, the distribution of free and methylated carboxyl groups within the polyGalA, molecule size, and sugar composition, may be related to how they function in the gut. Although pectins cannot be digested by human enzymes, commensal bacteria in the stomach can quickly break them down by producing SCFA and other metabolites. Pectin can reduce the production of ammonia in the intestine, delay gastric emptying and improve gastric tolerance [163]. Pectin regulates gut microbes by influencing intestinal homeostasis via intestine biodegradation [99]. Pectins can also increase intestinal immunity, intestinal integrity, mucosal proliferation, and probiotic *Lactobacillus* adherence to epithelial cells [164]. Numerous studies have described how pectins can promote the growth of particular bacterial populations, although the outcomes are not always consistent [165]. Hence, it is worth suggesting that more studies on a modified form of pectin (MP) should be given attention to considering that the DE, free level of carboxyl groups, size of molecules and sugar constituent may play some major role with positive outcomes affecting the gut microbiota.

Some studies reported various beneficial bacteria in the gut, such as *Bifidobacteria*, *Lactobacilli*, *Faecalibacterium prausnitzii*, *Roseburia* spp., and *Eubacterium rectale*, were activated by in vitro fermentations with pectins [44,166], while others found that *Bifidobacteria* and *Roseburia* levels remained the same or even dropped [167,168]. A study mentioned that the main pectin-degraders are *Bacteroides* and *Prevotella*, which have carbohydrate-active enzymes amongst others such as *Enterobacteriaceae* and *Clostridium* species [165]. These inconsistencies across research on the effects of pectin on microbial populations could be due to certain factors such as variations in the microbiota, enzyme capacities, and fermentation substrates. As a shift in the species-specific ability to degrade pectin by an enzyme is becoming substrate-dependent, the intensely competitive environment in faecal fermentations and preferential use of metabolites from LM pectin breakdown can be anticipated. Nevertheless, a significant rise in *Butyrivibrio* and *Lachnospira*, which have previously been demonstrated to be unable to break down pectins, may be related to metabolic cross-feeding interactions between the faecal microbiotas constituents [165,169,170]. In faecal fermentations and mixed cultures, pectins with lower DE and oligomeric size were preferentially digested and thus encouraged the growth of *Bifidobacteria* [171]. In recent studies, the levels of faecal *Prevotella* and *Lactobacillus* in piglets varied between the LMP and HMP [172]. Another study investigated the effect of the MCP alone and with or without probiotics on the mice's faecal lactobacilli. The faecal lactobacilli count in the MCP and probiotic-treated colon tumour mouse model increased by 10.2% after 4 weeks of treatment. The number of faecal lactobacilli in the MCP-treated group decreased by 0.6% below that of the control group which indicated that the faecal lactobacilli count was most likely influenced by the interaction of the colon microbiota with the probiotic bacteria, *L. acidophilus* ATCC 4356 supplemented with MCP [119]. Colon microflora responds dynamically to changes in dietary intake is supported by the variations in the number of faecal microflora found in the treated mice [173,174]. However, the disintegration of the MCP and resistant starch by

L. acidophilus ATCC 4356 and intestinal microflora could lead to the increased production of SFCAs, gases and butyrate. For colonic epithelial cells and faecal lactobacilli, butyrate is the preferred energy source. These SFCAs can induce bile salt hydrolase, which results in the formation of bile salts. The colonization of the *L. acidophilus* ATCC 4356 in the intestine would be antagonistic with the indigenous flora community, which grows and survives on macromolecules MCP and alginate. Individual differences in endogenous lactobacilli constitution have a substantial effect on the growth of exogenous lactobacilli. This shows that probiotic colonisation is linked to a steady indigenous lactobacilli community [175]. In a similar study, a charged modified citrus pectin-encapsulated probiotic supplementation positively modulated gut microbiota composition in high-fat diet-fed Wistar male rats [86].

Chronic inflammation, which has been associated with gut microbial dysbiosis, is related to the development of comorbidities associated with obesity [86]. Pectin fermentations have an impact on the diversity of bacterial taxa linked to microbiota dysbiosis in human disorders such as obesity and inflammatory bowel disease (IBD). It was demonstrated that the gut microbiota of people with obesity exhibited a bias that included increased levels of *Eubacterium, Roseburia, Dorea*, and *Ruminococcus* and decreased levels of *Faecalibacterium prausnitzii, Prevotella, Bacteroides*, and *Proteobacterial* genera [176,177]. As previously mentioned that shift in the species-specific ability to degrade pectin is becoming substrate-dependent, this indicates that specific pectins can influence these species. A study showed that fermentation of HMP rather than LMP could stimulate *F. prausnitzii* while *Prevotella copri*, a microorganism linked to induced insulin resistance in rats and rheumatoid arthritis in humans, was effectively reduced by LM citrus pectins as well as a higher level of *Coprococcus* in people with irritable bowel syndrome which is indicative of less severity [178–180]. Only a few research suggested a connection between the DE in pectins and the microbiota's makeup. *Prevotella* spp. enrichment was seen in the colonic microbiota of pigs given LMP and genus Bacteroides grew in faecal batch fermentations of LMP as opposed to HMP [165,172]. It is good knowledge that pectins' structural characteristics influence their ability to gel, viscosity, molecular conformation, and solubility. It is suggestive that these characteristics may affect how MP is utilized in the gut microbiota fermentations and how the interaction of gut bacteria and substrate are affected. Because LM pectins have a higher proportion of non-esterified carboxyl groups than HM pectins, it was observed that their surface charge was lower which might indicate a stronger electrostatic repulsion when interacting with bacterial cell walls [165]. Extensive studies and literature have revealed that bioactive substances influence the gut microbiota toward protective impact against gut illnesses such as colon cancer, obesity, diarrhoea, and IBD [127]. On the contrary, very little literature is on the function of gut microbiota dysbiosis as well as its diagnostic and prognostic relevance to MP. Understanding the connection and association between the DE in pectin and gut microbiota changes could result in the creation of a novel therapeutic strategy based on gut microbiota manipulation, such as employing MP.

6.5. Synergistic Effect

Over the recent years, MP has been employed in many pre-clinical and clinical drug therapy studies showing the bioactive function and ability of MP to prevent cancer. The majority of cancer-related morbidity and mortality is brought on by metastasis, which is when cancer spreads from the primary tumour's growing location to distant organs and tissues. Additionally, MP works well against several cancers, including breast, colon, and melanoma [181,182]. It is so interesting that the application of MP in cancer therapy became more acceptable with the growing knowledge that the galectins on the surface of cancer cells have a binding affinity for galactose-rich MCP, which inhibits or blocks cancer cell adhesion, aggregation, and metastasis [183]. The MCP has a fair amount of galactose and opposes the binding protein, Gal-3, to prevent cancer from metastasizing [184]. It is important to mention that a synergistic approach of MP delivery with other bioactive polymers improves its anti-cancer properties, hence its recent application in the biomedical and drug therapy industry is becoming widely accepted and gaining attention.

In a recent study, the effectiveness of combining ionized radiation and MCP on prostate cancer cells was assessed. A reduced Gal-3 and increased expression of the pro-apoptotic protein Bax with caspase-3 precursor cleavage were noted which causes downregulation of the DNA repair pathways. The ability of prostate cancer cells to spread metastatically was inhibited by MCP. These results establish MCP as a radiosensitizing drug that can increase IR cytotoxicity, overcome radioresistance, and lower clinical IR dose [185]. In a similar study, the combined impact of BreastDefend (BD) and ProstaCaid (polybotanical compounds) with MCP on invasive behaviour in breast and prostate cancers was investigated which synergistically inhibits the adhesion of these cells [186]. This combination of MCP and paclitaxel on apoptosis of human SKOV-3 ovarian cancer cells showed synergistic cytotoxic effects, resulting in a 3.9-fold increase in caspase-3 activity, a 75% reduction in cell viability and a 39% decreased substrate-dependent adhesion leading to the inhibition of galectin-3 [19]. In PCa (prostate cancer) cell lines (DU-145 and LNCaP), PectaSol's impact on Dox (Doxorubicin) cytotoxicity in terms of apoptosis and cell cycle alterations has been studied. In DU-145 and LNCaP cells, the combination of PectaSol with Dox led to viability values of 29.4 and 32.6% ($p < 0.001$). Effect of combining PectaSol with Dox on cell cycle arrest, apoptosis, and viability in DU-145 and LNCaP prostate cancer cell lines [21]. In another study, the synergy of a probiotic, *L. acidophilus* ATCC 4356 and MCP with alginate prevents tumour development in a colon cancer-induced mouse model by inhibiting Gal-3 and VEGF immunoexpression and decreasing tumour incidence. Although a suppressed Gal-3 expression with a low prevalence of precancerous lesions by the alginate probiotic treatment during carcinogenesis was observed. The combination of the probiotic and MCP was more efficient than either MCP or the alginate probiotic alone in decreasing Gal-3 expression in colonic carcinogenesis. This showed a significantly low immunoexpression of Gal-3 in the mucosal cells of the crypts than in the endothelial cells in all three treatment regimens. The bioactivity of MCP provides inhibition of vascular endothelial growth factor expression in endothelial cells through its galactoside-β moiety [128]. MCP prevented cardiac inflammation and fibrosis associated with an excess of aldosterone levels independently of blood pressure levels. In this mouse model with selective isoproterenol toxicity, galectin-3 inhibition by MCP and aldosterone opposition corrected ventricular systolic failure, inhibiting the formation of myocardial fibrosis in the heart [187,188]. The pleiotropic effects of MCP are suggestive of the potential antihypertensive effect of MCP against ACE-1 receptors and Ang II [17] though require more investigation. The antimicrobial and/or inhibition effect of MCP and cefotaxime against *Staphylococcus aureus* isolates at relatively low concentrations was noted [189]. Studies have repeatedly exhibited synergistic and additive actions of MP that boost the effectiveness of treatment and enhance therapeutic results as shown in Table 4.

Table 4. Synergistic health benefits of modified pectin.

MP	Disease Type	Model Used	Studied Type	Outcome	References
MCP and paclitaxel	Ovarian cancer	In vitro	Human SKOV-3 cells	Synergistic cytotoxic effects with an increase in caspase-3 activity, and reduced cell viability	[19]
MCP (PectaSol) and Dox	Prostate	In vitro	DU-145 and LNCaP cells	Dox and PectaSol's cumulative cytotoxicity impact quickly causes cell death in DU-145 cells through apoptosis and in LNCaP cells through cell cycle arrest.	[21]
MCP	Prostate	In vitro	LNCaP and PC3 cells	MCPs prevent MAP kinase from becoming activated, boost the expression of its pro-apoptotic protein downstream target Bim, and cause Caspase-3 to be cleaved in PC3 and CASP1.r	[22]

Table 4. *Cont.*

MP	Disease Type	Model Used	Studied Type	Outcome	References
MCP + *Lactobacillus paracasei* LPC-37 and *Bifidobacterium bifidum* ATCC 29521.	Prebiotic activity	In vitro	Broth cells	Prebiotic activity scores increases with selective growth of probiotic bacterial.	[75]
Charged MCP and *L. paracasei subsp. paracasei L. casei W8®; L. casei W8*	Obesity and gut disorder	In vivo	Wistar rats	Pectin-encapsulated probiotic supplementation positively modulated gut microbiota composition in HF-fed male rats	[86]
MCP + *L. acidophillus* ATCC 4356 + alginate	Azoxymethane-induced colon tumour	In vivo, In vitro	SGI, and Balb/c Mice	MCP and alginate significantly enhanced the viability of *L. acidophilus* ATCC 4356 compared to the control ($p < 0.05$) both in vitro and in vivo and increased faecal lactobacilli.	[119,120]
MCP + *L. acidophillus* ATCC 4356 + alginate	Colon cancer	In vivo	Balb/c Mice	Probiotics improve the bioactivity of MCP by chemopreventive effects against pre-cancerous colonic lesions and adenocarcinoma.	[128]
MCP and IR	Prostate	In vitro	PCa cells	MCP sensitizes prostate cancer cells towards radiotherapy enhancing cytotoxicity.	[185]
MCP + BreastDefend and ProstaCaid	Breast and prostate cancers	In vitro	Breast (MDA-MB-231) and prostate (PC-3) cancer cells	MCP reduces the metastatic characteristics of human breast and prostate cancer cells synergistically when combined with BD and PC, respectively.	[186]
MCP and cefotaxime	Antimicrobial resistance	In vitro	Assay	Some isolates of S. aureus are inhibited	[189]
MCP and Honokiol	Cancer and cardiovasular	In vitro	Assay/cell lines	Improved antioxidant and anti-inflammatory properties	[190]
MCP and perindopril	Myocardial fibrosis	In vivo	Rabbits	Perindopril and MCP significantly reduce myocardial fibrosis and ameliorate ischemic heart failure.	[191]

Abbreviations: MCP, Modified citrus pectin; SGI, Simulated gastrointestinal conditions.

6.6. Anti-Viral Effect

New and intriguing research on MP's impact revealed that the fragments can bind to the pro-metastatic protein Gal-3's carbohydrate recognition domain (CRD). Due to this, Gal-3 is less able to interact with other proteins and peptides, which reduces its ability to promote cell adhesion and migration, as seen in tumorigenesis and apoptosis [17,192]. As a result, it is possible that MP, by inhibiting Gal-3, might be employed in a possibly risk-free and non-toxic way to stop or lessen viral adhesion and viral-associated inflammatory responses that are targeted toward a therapeutic approach [193,194]. Recent studies have connected the effects of oral MCP ingestion to its particular molecular interaction with Gal-3, thus exploring its antiviral activity. A binding mediator known as Gal-3 has been found to facilitate viral attachment. The interaction of the viral protein with the cell receptors and adhesion factors during viral infection can be caused by the glycosylation of the outer membrane spike glycoprotein. As a sugar molecule with a high concentration of β-galactose, the CRD of Gal-3 has a strong attraction for β-galactosides. As a result, MP can firmly attach to the Gal-3-galactoside protein and control its bioactivity [183,195]. This prevents the viral cell from adhering to the host cell [93]. Unlocking the antiviral potential of MP has been made possible by the understanding of antiviral substances containing sugar or sugar analogues that may be employed to inhibit respiratory viruses such as coronavirus from adhering to its sugar co-receptor [196]. According to a study, plants can defend themselves against viral contamination by inhibiting virus-driven genes that are triggered by pectin methylesterase which might contain substances that work through

their host to inhibit viral infection [197]. With a selectivity value of greater than 20, a pectin polysaccharide significantly inhibited the herpes simplex virus type 2 (HSV-2) and poliovirus [198]. This further shows that pectin inhibits viral replication at the early stage by interacting with the cation amino acids glycoprotein-binding site in herpes simplex virus type 1 (HSV-1) and the anion sulphated/carboxyl group heparin–sulphate chains of the cell membrane [198,199]. The main viral surface antigen that neutralising antibodies can attack during an infection and block viral entry is the S glycoprotein on the N-terminal domain. It is important to note that numerous possible treatment targets by MP could be involved in viral attachment to cell surfaces for reproduction through viral spike proteins.

6.7. Other Applications

Pectin as a supplementary dietary fibre found in the cell wall of plants is a functional recipe in processed foods. Pectin in fruits such as apples, citrus, grapes, plums, and vegetables is consumed daily as a dietary fibre to prevent the occurrence of diseases such as diabetes, and cardiovascular and colorectal cancer [200]. As a soluble fibre, pectin has a water-retaining ability which makes it form a gel. This enables pectin to remove toxic waste from the colon and prevent constipation. Additionally, eating a diet high in soluble fibre, similarly to MP, causes an increase in the excretion of bile acids, which lowers cholesterol and lowers the risk of cardiovascular disease [201].

When extracted, they are used as oil-in-water emulsification in food formulation, water binders, stabilizers and thickening agents in the production of jams, jellies, fruit juices and milk drinks. MP is a high-value functional food ingredient utilized in the nutraceutical industries [202,203] and bioactive cells. MP's physicochemical characteristics, such as viscosity, molecular weight, DE, and the presence of acetylation can be linked to its ability to decrease cholesterol. According to studies, LM pectin does not cut cholesterol levels as effectively as high molecular weight HM pectin [99]. The contact time of drugs for obesity and eye therapies has improved because pectin may form gels in acidic conditions [201]. Treatments for obesity and weight loss may benefit from gels' tendency to swell in acidic environments. This is due to the gels' ability to promote fullness and a lack of appetite by swelling and adhering to the stomach's walls before digestion in the aqueous environment of gastric juices [1].

7. Conclusions and Future Directions

Research on pectin is expanding as it becomes more significant for many uses in the food and pharmaceutical industries as well as in biomedical applications [204]. It still needs to look into several details about stability, optimal molecular weight, and interactions with other molecules [205]. One of the cheapest, safest, and most potentially non-invasive methods of therapeutic additions for humans needed to activate the immunity of the body is the use of MP. The development of MP microbead could be a unique and efficient oral delivery system as well as a food supplement (when paired with health-promoting bacteria). More investigation into in vivo and preclinical model studies should be explored to determine its efficient route of action. Pharmaceuticals should explore the use of MP as a drug carrier since it is biodegradable, affordable, non-toxic, demonstrated efficiency, is simple to use, and is stable at low temperatures. The usage of MP can be a viable therapy that enhances the host's ability to fragment MCP bioactivity, protecting it against intestinal illnesses. The mechanism of assimilation of the fragment molecules accountable for MP bioactivity would be revealed by additional molecular analysis. MP has been demonstrated to be one of the most effective and naturally occurring anti-Gal-3 compounds. A possible therapeutic target against diseases has been highlighted via a new method using a Gal-3 inhibitor. The Gal-3 inhibitor's potential in the course of the disease has been demonstrated by MP, and new uses for this bioactive substance will continue to be discovered. In clinical experiments, several pharmacological bioactivities were discovered, including wound healing, myocardial fibrosis, cardiovascular fibrosis, antimetathesis, detoxification, anti-ulcer, anti-obesity, anticoagulant and cholesterol-lowering actions, and

lipase inhibition [17,206]. The recent use of MP in the food, agriculture, biomedical and pharmaceutical sectors to produce edible food coatings, bio-based antimicrobial films, and nanoparticles may be due to the degree of methyl-esterification and neutral sugar side chains in the structure. However, the extraction and modification techniques may affect these properties, as well as the therapeutic efficacy, can vary as a result of the modification. Hence, this is still a knowledge vacuum that has to be addressed, and new research should focus on it.

8. Perspectives

The degree of esterification, Mw, the content level of GalA and sugar constituents have a significant effect on the bioactivity and encapsulation delivery system of MP. The biological activity, gelation behaviour and micro delivery functions of MP are significantly impacted by the extraction technique, the source of pectin, modification strategies, and the structural complexity of pectin. Through the emerging extraction and modification including the technologies that are now available, the bioactivity of MP can be improved by targeting or promoting specific health benefits. Modification of the structure of pectin which affects the functionalities of the carboxyl groups needs be linked to a unique molecular structure to certain functionalities of MP targeting the RGI and/or the HG region depending on what function the modified pectin is expected to perform.

With the understanding that the HG region is very crucial to the gelling property of pectin and for emulsion, gel stability and encapsulation, the RGI region is more responsible for its anti-cancer and immune interaction effects. Attention should focus on modifying the pectin to favour encapsulation delivery system for probiotics, microbial materials, proteins, polyphenols and carrier of vaccine or as an adjuvant to boost the immune system through stimulation of anti-inflammatory cytokines and release of interleukins. This, however, requires more in vivo studies to further evaluate these therapeutic applications. The modification or alteration in the structure of pectin creates a carboxyl group on the galactan to interact more with Gal-3, the galactose-binding proteins which also increases the bioavailability of the free galactans. This significantly promotes the health-related benefits and therapeutic application of the MP as the case may be in some disease indications.

Pectin is also highly biodegradable and biocompatible, which makes it a fantastic carrier for colonic medications and bioactive compounds. HMPs are used in some applications as an encapsulating agent in drug administration because they have a larger molecular weight and poorer solubility in water. However, early release and coating degradation might be a challenge with HMP, hence, LMP should be utilised more frequently in this regard. LMP should be generated from HMP by breaking down the molecular weight of industrial pectin to create more chances for calcium to interact and bind with the carboxyl group, thus expanding the possibility of LMP binding as the concentration of calcium ions increases. As such, the synergistic combination of MP with other natural polymers, such as chitosan, or bioactive compounds improves the bioactive functions of MP and also avoids early release, increases gel resistance, decreases water solubility, reduces erosion capacity, and generates new materials with specific properties required for drug delivery. Technologies that are in development for extracting pectin have also been created to minimize harm to the chemical structure and composition while limiting environmental effects.

It is worth mentioning that pre-clinical studies on the modified form of pectin (MP) should be given more attention considering that the DE, free level of carboxyl groups, size of molecules and sugar constituent may play major roles with positive outcomes affecting the gut microbiota. MP can also increase intestinal immunity, intestinal integrity, mucosal proliferation, and probiotic adherence to epithelial cells.

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