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Review

Therapeutic and pharmaceutical benefits of native and modified plant pectin

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Plant pectin constitutes an important class of naturally occurring polysaccharides and are widely distributed in various fruits and vegetables consumed on a regular basis. These biomolecules are reported to exhibit a vast array of biological activities including effects on digestive system, chemo-preventive effect in colon cancer, regulation of blood cholesterol level and immune-potentiating effects. However, variation in spectrum of activity and efficacy occurs due to different sources of pectin and also different methods of extraction. Pectin modification by pH treatment, change in temperature or enzymatic modification methods can ensure derivatives with variable but defined degrees of esterification, customized physicochemical properties and improved pharmacological and therapeutic profile, mainly in cancer prevention and management. Pharmaceutical utility of plant pectin is attributed to the unique rheological behavior and gelling properties in aqueous medium and have been successfully employed in development of colon specific sustained release drug delivery systems and edible pectin films with stabilizing effect on entrapped labile molecules. The goal of the review article is to focus on the therapeutic and pharmaceutical benefits of native and modified pectin. Although, several milestones towards understanding the process of pectin modification have been established, most of the data generated till date are obtained from *in vitro* studies or on commercial varieties of modified pectin. Complete characterization of structure-activity relationships of modified pectin, well-planned *in vivo* investigations and optimization of pectin-based scaffolds for controlled and targeted drug delivery in oncotherapy are yet to be ascertained for enhancing the marketing potential of these renewable plant-derived biopolymers.

Key words: Citrus pectin, edible films, apoptosis, colon cancer, modified pectin.

INTRODUCTION

Pectin is a naturally occurring polysaccharide present in the cell walls of all terrestrial plants and literature survey reveals several investigations on pectin extracted from plants like citrus fruits, apple, pomace, sunflower heads, sugar beet waste, mango waste, banana peels, green tea, tomato, carrot, papaya, grapes, plums, blackberries, etc. (May, 1990; Sriamornsak, 2003; Ezugwu et al., 2012; Poiana et al., 2013; Plaza et al., 2013; Tyagi et al., 2015).

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Different methods of extraction have also been adopted to maximize the yield (Srivastava and Malviya, 2011). Pectin has gained wide acceptance in food and confectionery industry because of its gelling property, viscosity and stabilizing activity. It is essentially a linear chain of poly-α-(1,4)-D-galacturonic acid with variable degrees of methyl esterification, denoted as degree of esterification (DE). According to DE, commercial pectin can be classified as low-methoxyl (LM) pectin and high-methoxyl (HM) pectin. The degree of esterification is below 50% for LM-pectin.

In recent times, role of dietary components in cancer prevention is an area of increasing clinical and scientific research. Since, pectin is abundant, its link to health promoting effects should be well-elucidated. On the other hand, the unique rheological behavior of pectin renders it highly useful for pharmaceutical preparations. However, since the extraction conditions greatly affect the biological activity and gelation behavior of pectin, alternative approach is to modify their structure by suitable agents or methods. Modification can induce changes in therapeutic efficacy and also pharmaceutical applications.

The objective of the present review article is to summarize the therapeutic and pharmaceutical applications of native and modified plant pectin in general. It also aims to highlight the lacunae or gaps that need further research for better exploitation of these highly promising natural polysaccharides for benefit of mankind.

THERAPEUTIC EFFECTS OF NATIVE PECTIN

Effects on digestive system

Pectin is considered as a soluble dietary fiber as it remains undigested in the intestine but can be degraded by the colonic microflora. Reports of anti-diarrheal effect of oral pectin in infants and children are available in the literature. The effect is due to either preferential growth of good colonic bacteria such as *Biffidobacteria* and *Lactobacillus* over the bad bugs or due to little anti-bacterial activity against *Escherichia coli* as observed in *in vitro* studies. Incidences of intestinal infections are also lower (Leclere et al., 2013; Gama et al., 2015). Influence of pectin on gastric emptying time and rate of digestion can be used to exert beneficial effects during treatment of eating disorders. Regular intake of 20 g of apple pomace for 4 weeks doubled the gastric emptying time and consumption of meal fortified with pectin increased the time from 23 to 50 min. High viscosity and gelling behavior of pectin in aqueous medium retards the absorption of food from gastrointestinal tract by acting as a barrier between the digestive enzymes and food molecules and also through immobilization of food components in the intestine. Food consumption is also reduced due to ability of pectin to absorb large volumes of water producing a feeling of satiety (Leclere et al., 2013). Duodenal and gastric ulcers may also be treated by administration of a mixture of LM-pectin, aluminium hydroxide and magnesium hydroxide (Ogunka-Nnonka and Atinlikou, 2016). Pectin can be employed for detoxification of human body as it can promote absorption and removal of toxins, anabolic steroids, xenobiotics and metabolites from the body, which would have accumulated otherwise. Detoxifying capacity can be exploited by using pectin as prebiotics (Tyagi et al., 2015). It can effectively chelate and remove lead, mercury, arsenic and cadmium from gastrointestinal tract (GIT) via urinary excretion and has shown evidence of increasing fecal clearance of ^{137}Cs, a radioisotope produced during uranium fission (Leclere et al., 2013). These toxic heavy metal ions have higher affinity for pectin with low degree of esterification as compared to essential ions like calcium, magnesium and zinc. They are trapped in the “egg-box” structure of the pectin (Selected Modified Citrus Pectin/Alginate Research).

Effect on colon cancer

Since pectin is a dietary fiber, it is beneficial in preventing colon cancer. Rats exposed to well-known carcinogens such as 1,2-dimethylhydrazine and azoxymethane showed lesser number of smaller colon tumors when fed on pectin-rich diet, probably due to activation of apoptotic pathway. Apoptosis may have been induced by butyrate, end-product of pectin fermentation by colonic microflora. In an investigation on colon adenocarcinoma HT2 cells, incubation with pectin oligosaccharides increased apoptosis, DNA fragmentation and activity of caspases (Leclere et al., 2013; Gama et al., 2015).

Effect on blood cholesterol level

Effect of pectin on regulation of blood cholesterol level depends on viscosity of pectin. High viscosity preparations are assumed to exert more effect on lowering of blood cholesterol through interference with micelle formation, lowering the rate of diffusion of bile acid and cholesterol-containing micelles through bolus, reduction in uptake of cholesterol and bile acids, increased excretion of bile acids and neutral sterols in feces. Daily intake of pectin amounting to at least 6 g/day without any changes in diet or lifestyle can reduce cholesterol levels in subjects with normal as well as elevated lipid levels and thus can reduce the risk of coronary heart diseases. Anti-hyperlipidemic effect is comparatively less with low viscosity pectin. Plasma triglyceride concentration was unaffected. Hepatic cholesterol homeostasis in guinea pigs is altered by intake of pectin from prickly pear. No change in cholesterol absorption could be seen (Tyagi et al., 2015).

Effect on immune system

Anti-tumor activity of pectin components may be due to its immunostimulatory activity. Pectin polysaccharides isolated from Chinese medicinal plant have been reported to potentiate the immune functions of B lymphocytes, macrophages and "natural killer" cells. Immunopotentiating effect of HG-rich pectin polysaccharides from red ginseng is derived from nitric oxide production by macrophages. Degree of esterification plays a significant role in effect of pectin on LPS-activated macrophages. When DE of pectin is low, marked inhibition of iNOS and COX2 is observed. Moreover, MAPK phosphorylation, IKK kinase activity, activation of NF-KB and AP-1 activation are simultaneously inhibited. Highly esterified pectin binds to LPS and alters its binding to receptors (Leclere et al., 2013; Gama et al., 2015). Aqueous extract of mulberry fruits also produced pectic polysaccharides which demonstrated immune-modulatory activity through enhancement of macrophage function (Lee et al., 2013). Crude tea polysaccharide sub-fraction consisting mainly of HG pectin enhanced phagocytosis in HL-60 cells at a considerably low dose similar to that of LPS. There are reports of stimulating effect of HG pectin on M1-polarized macrophages, promotion of Th1-oriented adaptive immune response and induction of TNF-α secretion by human peripheral blood mononuclear cells (Chen et al., 2006; Wang et al., 2014).

Miscellaneous therapeutic effects

Hemorrhage or local bleeding can be effectively controlled by intravenous administration of pectin when quick onset of clotting is observed. However, pectin sulfate acts as anti-coagulant like heparin. Iron deficiency anemia can be treated by administration of degraded pectin-iron complex (Tyagi et al., 2015).

Orange peel pectin and apple pectin exhibited antimicrobial activity against methicillin-resistant *Staphylococcus aureus* and *E. coli* (Sood and Mathur, 2013). PectaSol C, pH-modified citrus pectin, is reported to exert marked immune-stimulating effect on different immune cell components of blood, such as activation of cytotoxic T cells, B cells and NK cells and thus has demonstrated cytotoxicity towards chronic myeloid leukemia K562 cells (Leclere et al., 2013).

HM pectin can be used to reduce incidences of gastric irritation observed with aspirin administration and can facilitate sustained release of the irritant molecule (Tyagi et al., 2015). Hydroxyl radical scavenging activity of different degree has been observed for hot pepper pectin obtained by treatment with sulfuric and hydrochloric acids. It has been noted that high molecular weight and low degree of esterification in hydrochloric acid-treated pectin can scavenge hydroxyl radicals more effectively at all concentrations studied. These data suggest that modified pectin may act as anti-oxidant but further investigations need to be carried out (Xu et al., 2016).

Mechanism of absorption of pectin *in vivo*

Bioavailability of pectin depends on its physicochemical characteristics like degree of esterification, molecular mass, structure, etc. Pectin fragments may be absorbed by passive absorption or active transport as across intestinal epithelial cells, GALT and M-cells. Modified pectin with low degree of esterification shows better anti-metastatic activity and also better metal detoxification property. Nature of surface charges on pectin molecule determines possibility of transport across Caco-2 cell monolayers. Endocytosis of modified pectin into liver cells occurs via asialoglycoprotein receptors. Hydrophilic modified pectin can move across cell membrane barrier only through intervention of active transporter (Zhang et al., 2015).

MODIFICATION OF PECTIN

Unmodified native pectin is a large complex macromolecule with molecular weight in the range of 60 to 300 kDa and with 70% esterification and hence cannot be digested till it gets to the intestine. But, enzymatic degradation results in smaller molecular weight derivatives (<15 kDa) with DE <5% which can be absorbed into systemic circulation to exert therapeutic benefits on multiple systems (Selected Modified Citrus Pectin/Alginate Research). Chemical modification of pectin can be achieved through saponification catalyzed by mineral acids, bases, salts of weak acids and primary aliphatic amines. Modification induced by pH changes can generate new fragments with altered solubility and biological activity. Care should be taken not to affect biodegradation (Jackson et al., 2007; Beneke et al., 2009). Biologically active portions in pectin are enriched under conditions which favour β-elimination such as acid hydrolysis, alkali treatment at 50 to 60°C. Elimination reaction reduces the length of pectin backbone, that is, induces depolymerisation, lowers DE through de-esterification of HG regions, preferentially removes arabinose residues and ultimately results in improved solubility (Leclere et al., 2013; Zhang et al., 2015).

Enzymatic modification of pectin has been brought about by endo-polygalacturonase (Endo-PG) which results in highly selective and specific structural changes in the polymer backbone. It causes depolymerisation by cleaving glycosidic linkages between two non-esterified α-D-galacturonic acid residues inside HG fragment. The end-products are rhamnogalacturonans rich in neutral sugars like L-arabinose and D-galactose. Action of Endo-PG on water extract of orange peel showed higher

immunopotentiating activity and anti-complementary activity than the native pectin. The modified pectin had higher percentage of D-galactose, L-rhamnose and D-xylose with galactose: arabinose ≥2.0 (Georgiev et al., 2012). Enzymatic modification process or so-called "green" method can successfully alter the macromolecular structure of pectin and can yield modified pectin with newer and improved properties and functionalities (Karaki et al., 2016).

Effect of modified pectin on cancers

Fractionated pectin powder, FPP, commercially available and obtained by heat treatment of citrus pectin has successfully induced apoptosis in androgen-responsive and androgen-independent human prostate cancer cells. However, pH-modified citrus pectin, PectaSol C failed to induce apoptotic activity. Removal of ester linkages in FPP by mild alkali treatment produced homogalacturonan oligosaccharides and loss in apoptotic activity. But, enzymatic treatment of FPP with pectin methylesterases and/or endopolygalacturonase did not induce any change in apoptotic potential indicating the role of base-sensitive linkage for the observed anticancer effect. Heat treatment of citrus pectin which causes β-elimination producing unsaturated sugar residues, also resulted in apoptotic potential suggesting specific structural requirements, produced by rearrangements or generation of new structures. It has been shown that active fragments are low molecular weight (10 to 20 kDa) oligosaccharides (Jackson et al., 2007). Programmed cell death of tumor cells via cell detachment from its matrix or tumor cell anoikis is another probable mechanism of antitumor effects of modified pectin (Zhang et al., 2015).

Modified citrus pectin (MCP), produced by pH modification has shown good evidences of anti-metastatic property both *in vitro* and *in vivo*. It competed with endogenous ligands of galectin-3 and interferes with cell-cell interaction. Oral administration of MCP to rats reduced the number of metastases in lungs in dose-dependent manner following injection with prostate cancer MAT-LyLu cells. Similarly, growth of breast (MDA-MB-435) and colon (LSLiM6) tumors implanted in NRC nu/nu mice was halted by MCP with decline in the number of metastases in lungs and lymph nodes. Balb/C mice fed on daily oral dose of MCP showed reduction in size of colon tumors (Leclere et al., 2013; Zhang et al., 2015).

Anti-tumor activity of modified pectin is assumed to reside in the terminal galactose and terminal structure of modified pectin. RG-1 domain may be responsible for eliciting activity (Zhang et al., 2015).

Galectin-3 targeting activity of MCP can prove helpful in reversing resistance of tumors to several chemotherapeutic agents. Re-sensitization of cancer cells to different cytotoxic agents such as doxorubicin, cisplatin, bortezomide and dexamethasone have been reported after administration of GCS-100, commercial form of MCP during investigations on multiple myeloma cells and prostate cancer cells (Leclere et al., 2013). Modified pectin can function as biological response modifier and can be involved in regulation of immunological system (Zhang et al., 2015).

Miscellaneous therapeutic effects of modified pectin

Combination of modified citrus pectin and low viscosity alginate removes toxic heavy metals and binds to chemical toxins but does not deplete the body of essential minerals, even when used for prolonged period. The beneficial combination also lowers incidences of ulcer (Selected Modified Citrus Pectin/Alginate Research). Oral administration of modified citrus pectin-alginate microbeads containing *Lactobacillus acidophilus* to mice increased fecal count of lactobacilli substantially after few days. This indicates that MCP-alginate microbeads can be used as probiotic for improving the microflora content in the gut (Beneke et al., 2009; Zhang et al., 2015; Odun-Ayo et al., 2017).

PHARMACEUTICAL PROPERTIES OF NATIVE AND MODIFIED PECTIN

Pectin is a complex carbohydrate containing high proportion of side chains which may interfere with intermolecular associations. Presence of side chains significantly affects rheological characteristics and also influences solubility, gelling, gelatinization, retrogradation, freeze-thaw stability, film formation interaction with other polymers, etc. Pectin solutions show concentration-dependent rheological behavior with Newtonian flow at dilute concentrations and pseudoplastic flow at intermediate concentrations. Factors affecting viscosity of pectin solution are molecular weight, degree of esterification, concentration of pectin, pH and presence of counterions in the medium (May, 1990; Majee et al., 2012; Tyagi et al., 2015; Gama et al., 2015; Majee et al., 2016).

Pharmaceutical applications of pectin can be attributed to its excellent gelling potential in aqueous solutions in the presence of sugar, acid or calcium ions. Gel strength depends on viscosity and solubility. Low solubility and high viscosity imply high gel strength. Gelation in the presence of sugars and in acidic pH can be said to occur through incomplete dehydration of the pectin molecule and it is somewhere in between solution and precipitation. Gelation ability differs with degree of esterification. In acidic pH, unesterified carboxyl groups present as partially ionized salts are converted to unionized carboxylic acid groups. This conversion leads to repulsion between pectin and water molecules and

simultaneous association between adjacent pectin molecules. Since, the number of carboxylic groups in HM-pectin is low, it fails to undergo gelation in the presence of metal ions, specially calcium. Aluminium or copper ions may induce precipitation under special circumstances. Pectin with higher degrees of methylation undergoes gelling at comparatively higher pH. Gel formation in LM-pectin is induced by cations which can be explained by “egg-box” model. In this model, junction zones are created by ordered, side-by-side intermolecular associations of galacturonans, linked through electrostatic and ionic bonding of carboxyl groups. Though this structure can accommodate amide groups, no improvement in strength of junction zone can be achieved. Stability of LM-pectin and LM-amidated pectin is comparatively greater than HM-pectin at room temperature as well as in humid and warm conditions (May, 1990; Sriamornsak, 2003; Tyagi et al., 2015). HM-pectin is very sensitive to changes in pH or temperature when chain cleavage occurs with subsequent loss in viscosity.

Pectin-based nanoparticulate delivery systems for 5-fluorouracil can be used for liver targeting in treatment of hepatocellular carcinoma since galactose residues on RG-I side chains in the polymer backbone act as natural targeting ligands for over-expressed asialoglycoprotein receptor (ASGPR), lactose-binding lectin on hepatic cell surface. Nanoparticles had a prolonged half-life in the body fluids as compared to free drug when tested in Sprague-Dawley rats and Kunming mice (Yu et al., 2014; Zhang et al., 2015).

Pectin can be employed in the design of sustained release colon-specific drug delivery matrix tablets. Calcium pectinate used in matrix tablets is degraded only by colonic pectinolytic enzymes and not by gastric or intestinal enzymes. Pectin-xyloglucan complex can be used to formulate *in situ* gelling system with sustained drug release profile. It also finds applications in development of ophthalmic systems and matrix type transdermal patches (Sriamornsak, 2003; Beneke et al., 2009; Majee et al., 2016).

Stable canola oil emulsions have been prepared using 2% hot pepper pectin solution as emulsifying agent. Emulsifying ability and stability of emulsion were affected by concentration of pectin and type of acid used for treatment of pectin (Xu et al., 2016).

Pectic enzyme treated citrus pectin has demonstrated potential to be used as an antioxidant for soy protein isolate-stabilized oil-in-water emulsion. Trolox equivalent antioxidant capacity and DPPH radical scavenging activity of the enzyme modified pectin were higher than that of untreated native citrus pectin. The amount of secondary oxidation products (thiobarbituric acid reactive substances) produced as a result of lipid oxidation was also less with enzyme modified pectin. The two varieties of pectin differed in their molecular weights and degree of esterification, the modified one having lower values for both properties. Mixture of modified and native pectin imparted greater emulsifying capacity and stability to the o/w emulsion under investigation (Huang et al., 2011).

Pectin films can be used for incorporation and stabilization of natural extracts, vitamins, colorants, flavoring agents, spices and thus can be used for antimicrobial, nutritional and antioxidant activities (Kaliana et al., 2015). Low-methoxyl amidated pectin could retain maximum color, maintain storage stability of incorporated bioactives and demonstrate highest antioxidant capacity as compared to low-methoxyl and high-methoxyl pectin (Poiana et al., 2013). Edible pectin films have been prepared with improved physico-mechanical properties by incorporation of plasticizers and emulsifiers (Espitia et al., 2014). The water vapor permeability and rigidity of pectin/papaya puree edible films can be significantly altered by incorporation of cinnamaldehyde nanoemulsions which also imparted antimicrobial property to the films (Otoni et al., 2014).

There are several reports of favorable interactions between pectin and other hydrophilic polymeric colloids such as gelatin, agar-agar, alginate, guar gum, locust bean gum, starch, oxidized starch, potato maltodextrin, gum arabic and also with proteins, However, gel setting temperature, water binding capacity, nature of gelation, the gel strength, swelling behavior, stability vary with the copolymer added (Jackson et al., 2007; Tyagi et al., 2015; Xiong et al., 2015; Xu et al., 2016).

FUTURE SCOPE

Different extraction protocols for plant pectin can produce significant changes in their effectiveness in inducing apoptosis in several cancers and also anti-metastatic activity. Findings from different studies indicate that actually, small pectin fragments may be responsible for anti-cancer activity (Jackson et al., 2007). Plant pectin is reported to exert wide range of immunomodulatory activities depending on the source and the sub-fractions present. These sub-fractions may be used in the future to control several infections (Wang et al., 2014). Probiotic activity of plant pectin has been proved *in vitro* but no suitable experimental protocol is available yet to provide *in vivo* sampling and to actually identify sites of colonization of beneficial bacteria in the gut (Odun-Ayo et al., 2017). Better understanding of structure-activity relationships of modified pectin is necessary to achieve consistent pharmacological and therapeutic benefits as well as to design and optimize pectin-based scaffolds for controlled and targeted drug delivery in oncotherapy. Molecular characterization and detailed structural elucidation of the various fragments and sub-fractions of the biopolymer will illustrate the mechanism of uptake and *in vivo* utilization for eliciting biological activity. Future studies in these directions will enhance the marketing potential of pectin obtained from renewable sources and also modified pectin produced by various strategies.

CONCLUSION

Pectin is abundant in plant-based diets and is found to exhibit a number of pharmacological activities with positive effects on cancer prevention or as anti-metastatic agent. Modification of pectin can produce significant changes in bioactivity and pharmaceutical properties as degree of esterification is altered. Although, detailed structural elucidation of modified pectin is yet to be obtained, it shows immense potential for betterment of human life.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests

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