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OVERVIEW OF THE PHARMACOLOGICAL USE OF PECTINS AND PECTIN-CONTAINING SUBSTANCES: RECENT ACHIEVEMENTS AND PROSPECTS

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ABSTRACT

This paper is an overview on the Pectins which are a group of polysaccharides from plant cells. Structural diversity makes functionality of the pectins versatile with a variety of biological, techno-functional, biomedical, and pharmaceutical properties. Nearly all the plants contain pectin, however, the majority of it is used commercially and is derived from citrus fruits, specifically oranges, lemons, grapefruit, and apples. Commercial production is judged on new features and applications in addition to economics. Recently, there has been an effort to find new sources of pectin, such as using the leftovers from the processing of pulp from sugar beet, mango, and sunflower. Pectin substances can affect the human body as follows: prebiotic effect, cholesterol reduction, anti-inflammatory and antimicrobial effect, antitumor effect, biosorbent, transportation of drugs. This article's goal is to discuss pectin application techniques and pectin-containing products. The prospects of further development and use of these biopolymers are also considered.

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Introduction

Pectin is a natural substance that is found in fruits, berries, vegetables, and some other fetuses. Pectin polysaccharides are formed by galacturonic acid residues. They belong to the group of water-soluble carbohydrates that are found in the cell membranes and intercellular tissues of some plants.

Pectin contains smooth areas (so-called linear areas) and branched areas **(Figure 1)**.

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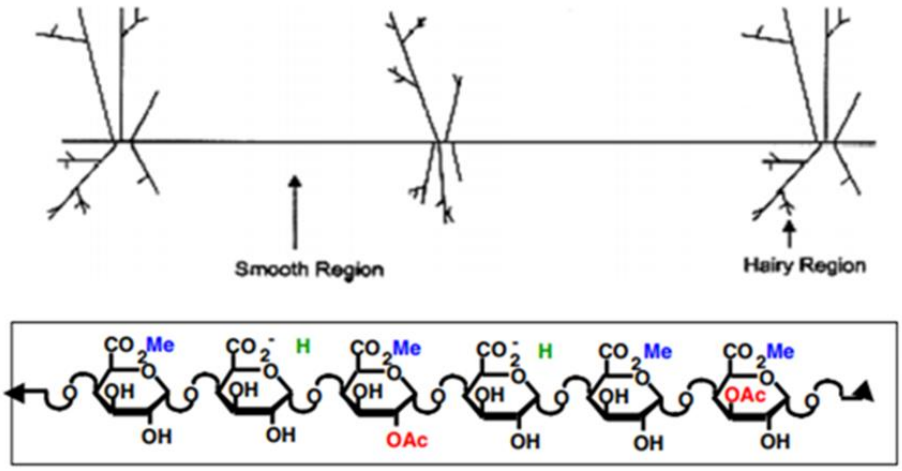

Figure 1. Pectin organization model (above) [1] and the structure of the smooth region is homogalacturonane (below) [2]

There are two distinct structural forms of galacturonic acid, which makes up the core of pectins. All varieties of pectins contain three polysaccharide domains that are built on top of them.

Homogalacturonan (HGA), rhamnogalacturonan-I (RGI), and rhamnogalacturonan-II are three such domains (RG-II). Between the primary cell wall and the middle lamella, a dense network can be created by covalently connecting these three domains.

The linear homopolymer homomogalacturonane (HGA) is made up of D-galacturonic acid residues connected by glucoside linkages of the α-1,4 type. It makes up around 65% of pectins and can contain up to 200 galacturonic acid residues. It is repeated in the structure of many pectin molecules. The Golgi complex of plant cells is where this polysaccharide is made.

The addition of an acetyl group to carbon 3 or carbon 2 is another change that galacturonic acid residues in the homogalacturonic domain may experience.

Furthermore, some pectins have xylose substitutions on carbon 3 of some of their residues, resulting in the xylogalacturonane domain.

Rhamnogalacturonan-I (RG-I) is a heteropolysaccharide consisting of just under 100 repeats of a disaccharide consisting of L-rhamnose and D-galacturonic acid. It makes up 20 to 35% of pectin. Most of the rhamnosyl residues in its main chain have side chains that contain separate, linear, or branched residues of L-arabinofuranose and D-galactopyranose. They may also contain fucose residues, glucose and methylated glucose residues.

The most complex pectin, rhamnogalacturonan II (RG-II), accounts for only 10% of plant cellular pectins. Its homogalacturonic skeleton, which is composed of at least 8 D-galacturonic acid residues connected by 1, 4-bonds, forms the basis of its very conservative structure.

More than 20 different forms of side chain bonds join the branches of these residues, which contain more than 12 different types of sugars. The two sections of rhamnogalacturonan-II are typically found as a dimer, with a borate-diol ether bond joining the two components. The polymer remnants of a-1, 4-bound D-galacturonic acid (GalpA), some of which are partially esterified with methanol and can be esterified with acetyl groups, make up the majority of the smooth areas. As a key factor in influencing pectin's solubility, gelation, and film-forming capabilities, the degree of esterification (DE) of galacturonic acid residues is crucial [3].

Thanks to such significant design variations, pectins have many unique functions:

- biological (plant protection, nutrient supply, etc.);
- technofunctional (gelation, emulsification, stabilization, thickening, film formation, etc.);
- Biomedical and pharmaceutical (have probiotic, antimicrobial, antioxidant, antitumor, etc. properties). The functionality of pectin is closely related to its structure [4].

Pectin is a complex biopolymer in structure. Polysaccharides are synthesized in Golgi bubbles. The Golgi complex is formed by intracellular membranes forming cisterns, vesicles, and tubules. Several parallel cisterns form dictyosomes [5]. The model confirms that pectin biosynthesis occurs in the cytosols of cells. The biosynthesis of pectin requires a large number of enzymes, due to the complexity of its structure. Directly, the synthesis of pectin is carried out in the cytosol of cells. The authors [6] estimated that the biosynthesis of HG, RG-I, and RG-II will require about 67 enzymes (for example, glycosyltransferases, methyltransferases, and acetyltransferases).

It is known that HG and RG-II are covalently bonded to the cell wall as a result of research on the structure of pectin and its biochemical characteristics. Additionally, the synthesis of RG-II can start with HG [3].

Pectin is found in some form or another in almost all plants, but in commercial production, it is mostly extracted from apples, grapes, and citrus fruits. Pectin content in dried apple pulp is typically 20%, but that in citrus peel is approximately 35% [7, 8].

The use of waste from the processing of sunflower, mango, and sugar beet pulp is one recent effort to find new sources of pectin [9].
Depending on the circumstances of the extraction, the authors [10] observed a yield of up to 23% pectin in sugar beet. But sugar beet pectin has a lower molecular weight and a larger number of acetyl groups, so the gelling ability is lower.
Special conditions are required for the gelation of HM pectins [11]:

- pH below normal (2.5-3.5);
- the presence of sucrose (55-75%). As a rule, HM-pectins are soluble in high temperature water. They often contain a dispersing agent to prevent the formation of lumps.

Independent of the amount of sugar present, LM pectins gel. Compared to HM pectins, they are more heat- and moisture-resistant [12]. LM pectins' capacity to form gels improves as the level of methylation is reduced.
Let's examine the impact of pectin and pectin compounds on all areas of human activity in more detail.

Prebiotic Effect

The effect on the body of prebiotics derived from pectins will largely depend on their physical and chemical properties. At the same time, both the consumption and distribution of metabolic products and other effects will differ.
The authors [13] have demonstrated that apple pectin is an effective remedy for diarrhea.
Since pectin is a water-soluble fiber, when mixed with water it forms a gel and also stimulates the development of beneficial intestinal microflora, which ultimately increases the volume of stool. In addition, pectin counteracts bacteria such as Salmonella, Shigella, Klebsiella, Enterobacter, Proteus, and Cytobacter [14, 15].
Since the essence of the fight against constipation is reduced to the same mechanisms (water absorption and the development of beneficial intestinal microflora), then pectin shows its effectiveness in these cases.
It is a fact that food pectin is able to stimulate the proliferation on intestinal cells and the activity of enzymes of the border membrane [16]. Without mentioning diarrhea and obesity, the primary byproducts of intestinal pectin fermentation in the form of acetate, propionate, and butyrate play a significant role in the prevention and treatment of numerous gastrointestinal illnesses, ulcers, and cancer.
Pectin sources have a considerable impact on the prebiotic effect on different bacterial strains, according to certain authors [17] who compared the prebiotic activity of several pectin polysaccharides.
The results showed that when potential prebiotics (pectin) were used and placed in a nutrient medium together with living cells, the number of living cells increased.
The authors [18] investigated pectin-induced changes in the gut microbiota and their effect on the production of short-chain fatty acids. Pectin decomposition was observed in all three donors. The results show that pectin fermentation increases the number of bacteria belonging to the Clostridium cluster (Lachnospira, Dorea, and Clostridium), with a greater increase in Lachnospira. The results also confirm that the fermentation of pectin leads to the formation of acetate and butyrate.
The review article [19] considers the effect of pectins as prebiotics. Knowing that prebiotic oligosaccharides give functional properties to products, efforts should be made to increase the fiber content and indigestible oligosaccharides in common foods to help consumers achieve the recommended prebiotic content in their diets. The work [20] examined the effect of pectin as a dietary fiber and a prebiotic beneficial to health. The article notes that in 2010, the European Food Safety Authority (EFSA) recognized the scientific validity of the use of pectin as a dietary supplement for nutrition and health improvement.

Reduction of Cholesterol

In the digestive system, pectin is able to collect various molecules and remove them through the intestines. One of these molecules is cholesterol. Pectin binds to cholesterol and removes it from the body before cholesterol is absorbed into the intestinal walls [21].
The study of the mutual behavior of pectin and cholesterol in the human body has been conducted over the past many years on thousands of patients. High cholesterol is the cause of many diseases (including cardiovascular ones), which subsequently often lead to heart attacks. The consumption of pectin in sufficient quantities allows one to reduce the content of total cholesterol in the body, in particular low-density lipoproteins (LDL).
According to some authors, pectin acts in three separate ways, each of which explains why total cholesterol and LDL levels have decreased. First, it prevents the reabsorption of bile salts. Second, pectin's high viscosity may have an impact on the glycemic response, slowing glucose uptake. Third, pectin produces short-chain fatty acids, particularly propionate, which can prevent the production of cholesterol in the liver by selective fermentation of fiber in the colon (probiotic action) [22].

Anti-Inflammatory, Antimicrobial Effect

Butyrate is one of the main metabolites of pectin, it acts as the main source of energy for colonocytes (intestinal cells), which triggers their differentiation and apoptosis [23]. It has a strong anti-inflammatory effect, inhibiting the activation of the inflammatory component of cellular signals.
In addition, modified pectin is able to bind and block the action of galectin-3 in the human body. Which, undoubtedly, has a beneficial effect on the state of the body. Galectin-3 is a carbohydrate-binding protein (lectin). Excess galectin-3 is associated with inflammation, fibrosis, heart disease, stroke, cancer and other pathologies [24].

Application as a Biosorbent

Heavy metals constantly entering the environment from various sources, such as industrial and agricultural waste, pose threats to the ecosystem as a whole and to human health in particular. Some authors distinguish a number of biosorbents based on pectin, the main property of which is the removal of heavy metals [25]. Industrial production of pectin comes from common and inexpensive vegetables and fruits, as well as from their processed products (apple and citrus peel). Biosorbents based on pectin will mainly be obtained in the form of round balls using calcium ions as a crosslinking agent.

Pectin has the ability to bind metals and promotes the excretion of heavy metal ions. In fact, it is a good substitute for conventional chelators, and it has no risks and side effects. Metals bind to pectin in the digestive tract and are excreted from the human body before they have time to be absorbed by the intestines [26, 27].

Antitumor Agent

Some authors believe that polysaccharides in pectins can have an immunostimulating effect on the human body. A striking example of a source of such polysaccharides (angelans) is the Chinese plant Angelica gigas. The immune capabilities of dendritic cells, macrophages, natural killer cells, and B- and T-lymphocytes can all be improved by angelinas, which generally have a highly positive impact on human immunity. This increases immune activity against tumor cells [28].

More detailed studies have shown that pectin blocks the pleiotropic activity of galectin-3 in cancer cells by reducing metastasis, angiogenesis and even tumor growth. The region of rhamnogalacturonan-I (RG-I) responsible for binding to and inhibiting galectin-3 was located by the authors [29, 30]. Eliaz *et al*. It has been shown that pectin can be an effective remedy against any of the four main stages of the development of malignant tumors affected by Galectin-3 [31].

Pectin as a Transport for the Delivery of Medicines

Being an organic polymer, pectin is an ideal means for drug delivery by encapsulation. The distinctive qualities of pectin – biocompatibility, mucoadhesiveness, safety, inertia, and the capacity to gel in acidic environments – lead to this conclusion [32, 33].

Some scientists have investigated the release of theophylline in an acidic environment. At the same time, the drug itself was in a capsule made of a two-layer film (a layer of pectin and a layer of calcium pectinate).

In addition, the delivery of the antitumor drug rutin in a capsule of low-methoxyl pectin was investigated. The results obtained demonstrated a higher anticancer activity of the new drug than the non-encapsulated rutin [34, 35].

The use of pectin has been evaluated in the treatment of eye diseases due to improved contact time and penetration of the drug into the eye.

The resulting pectin gel was applied directly to the eyes to treat them in the patents Ni and Yates were granted [36]. The gel provided delivery of drugs piroxicam and baricitinib. It has been shown that this system can provide high bioavailability and reduce some of the disadvantages of other ophthalmic systems [37].

Recently developed pectin composites for oral and nasal drug delivery have many improved properties compared to existing formulations without pectin. They include:

1. Higher drug loading efficiency;
2. Less release of drugs before delivery to the target tissue;
3. Greater efficiency for controlled release of peptide and protein preparations;
4. Increased biocompatibility, since only biopolymers are used for the manufacture of composites.

Drug administration via the nasal cavity is an alternative to injection. In-depth research is currently being done on nasal medication administration for systemic drug delivery when fast drug release is necessary [38, 39].

Fentanyl by applying an aqueous solution to the mucous membrane surface, a new pectin-based delivery technique known as pectin nasal spray causes a regulated absorption of fentanyl. Nasal spray fentanyl pectin quickly relieves pain and has a duration of action [40].

Conclusion

Thus, pectin is a unique polysaccharide that demonstrates a number of properties: 1) biological - cell growth, protection, etc., 2) techno-functional - gelation, emulsification, stabilization, 3) biomedical: it supports the primary bodily systems that regulate the digestive tract, cardiovascular system, redox balance, basic metabolism, development and growth, cognitive performance, and appetite; it lowers blood cholesterol levels; and it has antimicrobial and antitumor effects; it can ensure the balanced operation of the human body; 4) pharmaceutical: it is capable of delivering drugs to target organs.

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