

Pectin-Based Nanomaterials as a Universal Polymer for Type 2 Diabetes Management

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Abstract

Type 2 diabetes mellitus (T2DM) is characterized by insufficient tissue insulin sensitivity, insufficient compensatory insulin secretory response, and insufficient insulin production by pancreatic islet cells, which account for more than 90% of all instances of diabetes mellitus, and defects in any of the mechanisms at play may cause a metabolic imbalance that results in the development of T2DM. By getting around several delivery limitations, nanomedicine can effectively increase the efficacy of oral drug administration. According to reports, nanostructures are absorbed 15–250 times more readily than microparticles. Furthermore, nanostructures are constantly used to maintain the release of drugs that are encapsulated to lower doses and dosage frequency, improving patient compliance and reducing adverse effects. Pectin is a biocompatible polysaccharide with a natural biological activity, which pectin in rats with type 2 diabetes was discovered to have potent hypoglycemic, antioxidant, immunomodulating, and anticancer properties that improved diabetic conditions and consequences, reduced insulin resistance, improved blood lipid levels, and reduced liver glycogen content, glucose tolerance, and glucose levels. As a result, the purpose of this article was to evaluate the background materials on the current condition of the scientific literature in this field of study and to review the employment feasibility as well as pectin-modified nanomaterial toward T2DM treatment because it has the ability to reduce insulin secretion and/or blood glucose levels following a sugar load.

Keywords: Apple pomace, diabetes mellitus type 2, nanomedicine, nanoparticles, nanotechnology, pectin

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders marked by decreased insulin production, ineffective insulin utilization, or both. Chronic hyperglycemia exposure is a significant risk factor for developing cardiovascular disease, as well as other complications such as stroke, amputation, blindness, and depression. The significance of insulin as an anabolic hormone leads to metabolic irregularities in carbohydrates, lipids, and proteins.^[1] Microvascular complications such as nephropathy, retinopathy, and peripheral neuropathy can also result from chronic hyperglycemia exposure.^[2] An increasing proportion of pregnancies was developing this issue as a result of the rising frequency of type 2 diabetes in general and in younger persons in particular.^[3] In addition to being one of the top 10 causes of mortality, diabetes, together with three other major chronic diseases cardiovascular

disease, cancer, and respiratory diseases, accounts for nearly 80% of all fatalities in recent years, rising grave reservations about its impact on global health. Of the world's population, 9.3%, or 463 million individuals aged 20–79 years, or one in every 11 adults, had diabetes in 2019.^[2]

Over 90% of diabetes mellitus cases are type 2 diabetes mellitus (T2DM), a condition marked by deficient insulin secretion by pancreatic islet β -cells, tissue insulin resistance (IR), and an inadequate compensatory insulin secretory response. A metabolic imbalance that results in the

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pathogenesis of T2DM might be caused by abnormalities in any of the contributing pathways.^[4] Hyperglycemia is caused when insulin secretion is insufficient to maintain normal glucose levels as the sickness develops, which leads to the condition known as hyperglycemia. The majority of people who have T2DM are either obese or have a higher amount of body fat than is healthy, most noticeably in the abdominal region.^[5] Adipokine dysregulation and increased release of free fatty acids are only two examples of the numerous inflammatory pathways that adipose tissue uses to induce IR in this state. The prevalence and incidence of T2DM have doubled worldwide because of the growth in obesity, sedentary behavior, high-calorie diets, and aging of the population.^[5]

Insulin secretion dysfunction, IR in muscle, the liver, and adipocytes, and anomalies in splanchnic glucose uptake are all signs of glucose homeostasis problems T2DM individuals.^[6] As a result of decreased insulin production caused by β -cell malfunction, β -cell dysfunction is typically more severe than IR, even though both processes occur early in the pathophysiology and contribute to the onset of the illness. However, hyperglycemia is increased in the presence of both IR and β -cell dysfunction, causing T2DM to advance.^[7,8]

DIABETES MELLITUS AND NANOMEDICINE

Nanotechnology is the study of materials’ characteristics and uses, between 1 and 100nm in size. The qualities of the material alter, and specific features emerge when it approaches the nanoscale level.^[9] The substance is made up of macroscopic components, molecules, and atoms. The proportionate rise in surface area is the primary characteristic that differentiates nanoparticles from bulk materials; more specifically, the surface of ultrafine particles is covered with a ladder structure that represents restless atoms with high surface energy. Because of their particle sizes, the atoms may readily attach to other atoms and create huge surface-active atoms. Its use in medicine is mostly focused on altering the surface of nanoparticles by utilizing their special qualities to provide targeted, regulated release, simple-to-detect drug transport carriers, and a novel technique for treating local lesions. Nanotechnology is therefore essential for regenerative medicine.^[9]

By getting around several delivery limitations, oral drug delivery has been demonstrated to be much more effective when using nanomedicine.^[10] The uptake of nanostructures has been demonstrated to be 15–250 times greater than that of microparticles.^[11] Additionally, in order to reduce dosages and dosing frequency, increase patient compliance, and lessen side effects, nanostructures are frequently utilized to sustain the release of medications that are encapsulated.^[12] The various oral nanodelivery techniques of phytocompounds for the preclinical treatment of T2DM have not yet been thoroughly studied.

Table 1: Some diabetes issues and potential nanomedicine solutions

Measurement issues	Solutions based on nanometry
Continuous blood glucoses monitoring: Stable implanted enzyme electrodes Noninvasive monitoring	Biocompatible nanofilms, smart tattoo of glucose nanosensors
Improved diagnosis/monitoring complications: Targeted molecular imaging Understanding mechanisms	near-infrared quantum dots, gold nanoparticles Single-molecule detection
Therapy problems Improved insulin delivery: Islet cell transplantation Oral insulin Closed-loop insulin delivery	Nanotherapeutic solutions Islet nanoencapsulation Insulin nanoparticles, artificial nano pancreas

Nanotechnology applications in diabetes are still in their early stages concerning clinical needs and vision.^[13] As is frequently the case in the development of medical technology, technological advancements in areas such as biomaterial, analytical science, and engineering are happening more quickly than and frequently without any consideration for how they will be translated into the standard clinical practices. Therefore, it is helpful to appraise some of the current issues with diabetes management and the potentials that nanomedicine offers to address them [Table 1].^[13]

NANOTECHNOLOGY APPLICATIONS IN DIAGNOSTICS

The explanation of nanotechnologies includes a discussion of certain applications. In contrast to fixed assays using DNA chips, the microbeads offer flexible assays that allow for the screening of various genes using various beads according to the findings of earlier experiments. Immunohistochemistry, genotyping, biomarker studies, early detection of cancer, and the detection of infectious microorganisms are a few significant areas of therapeutically useful application.^[14] For the greatest feasible patient results, diabetes must be accurately and quickly diagnosed. For instance, early and reliable diagnostic testing can identify patients who would benefit from the early use of medication or lifestyle management techniques and could stop dysglycemia or even the beginning of an illness. A variety of disease-related consequences were shown to be averted or delayed by early glycemic control in previous research.^[15] Traditional methods of testing, such as evaluating hemoglobin A1c levels, oral glucose tolerance tests, or fasting blood glucose levels, sometimes fall short in this regard when the cause of diabetes is unclear; measuring autoantibodies in the context of clinical trials is frequently used as a diagnostic test to identify individuals who are at high risk for developing it. In the clinical setting, autoantibodies are also occasionally used to identify individuals who

have type 1 diabetes.^[16] These techniques, which some patients find uncomfortable, rely on antibody titers or glucose measurements, which can fluctuate based on a number of factors, including age, the timing of the test, and other physiological parameters. Additionally, the appearance of illness signs including hyperglycemia prevents early intervention because it frequently is not clinically apparent until several years after the onset of the illness. Different kinds of nanotechnologies have been created to potentially enable early and noninvasive diagnosis of diabetes in order to address the shortcomings of commonly used diagnostic instruments.^[16]

USES OF NANOTECHNOLOGY IN MONITORING

Traditional glucose meters need patients to regularly prick themselves with a finger; recording variations in glucose levels throughout the day is the most popular method of monitoring diabetes. Although tried and true, this approach has several disadvantages, such as low patient compliance and inaccurate glucose readings caused by some variables, such as age, mealtimes, etc.^[17] Standard GM cannot be performed while engaging in many routine tasks, such as driving or sleeping. As a result, various attempts to provide a hassle-free approach for GM have been developed during the past three decades. However, because conventional monitoring techniques are intermittent, patients are at risk for major problems because they could ignore potentially harmful glucose changes between testing. Eventually, this idea made sense and gave rise to continuous GM systems, which can continuously provide GM for a maximum of 10 days. Implantable biosensors were the key to making this vision a reality.^[16] Amperometric subcutaneously implanted sensors were a part of the initial generation of these devices. These sensors generate a quantifiable electric current based on glucose levels.^[18] These devices, though a step toward continuous GM, have a number of drawbacks, such as (1) a loss of stability caused by sensor drift and signal lag; (2) the requirement for daily calibration and subcutaneous insertion procedures every week; and (3) their high sensitivity to variations in a variety of physiological conditions, including pH and temperature. Biosensors built with nanotechnology could be able to get beyond these restrictions.^[18,19]

THE STRUCTURE AND PHYSICOCHEMICAL PROPERTIES OF PECTIN

Depending on its source or technique of extraction, pectin, a biocompatible polysaccharide with inherent biological activity, may display various structural characteristics. The impact of apple pectin from two distinct apple varieties as a lipase inhibitor. The culled fruits, mechanically damaged fruits, as well as the peel, core, and pomace of processed fruits, make up the fruit wastes

from agro-industries. One significant biopolymer that is mainly recovered from citrus and apple wastes is pectin. Several methods have been documented for removing pectin from fruit waste.^[20] Pectin is sensitive to enzymatic, chemical, and/or physical alterations.^[21] The present apple pomace (14%), and to a smaller extent, is the primary source of pectin for commercial use. However, the long-term commercial success of pectin has demonstrated the significance of using significant quantities of byproducts from fruits and vegetables as raw materials to create products with added value. Conventional methods or a mixture of cutting-edge technologies, such as ultrasound, microwaves, and enzymatic extraction, or their 11, might be used to carry out the pectin extraction.^[22] Commercial pectin is primarily derived from apple pomace and citrus peels, byproducts of the cider or juice industries. Pectin is currently being extracted from other byproducts, including sugars, beet pulpes, sunflowers head leftovers, passion fruit, and pomelo. Due to differences in chemical composition, molecular size, and the degree of esterification values, pectin from various plant species demonstrated a variety of qualities. It was further impacted by the extraction procedures, which were frequently carried out at high temperatures in a concentrated acidic media. By de-esterifying and depolymerizing, the traditional extraction techniques significantly damage the molecular structure of pectin. Additionally, technologies for extracting pectin that are still under development have been created to protect the composition and chemical structures while minimizing environmental impacts.^[21,23]

The structure of pectin is shown in Figure 1 because pectin can alter during plant separation, storage, and processing, making its determination extremely challenging. The primary components may also be accompanied by impurities.^[24] Right now, pectins are a kind of polysaccharides that contain a lot of galacturonic acid (GalA). Homogalacturonan, rhamnogalacturonan-I (RG-I), and rhamnogalacturonan-II (RG-II) are three polysaccharide domains that are assumed to be present in all pectin species and including GalA.^[25] When compared with the more complicated RG-II structure, which has been found in the main cell wall of certain plants, RG-I is found in the highly branching region and contains a greater number of side chains of α -1,2-linked residues of L-rhamnopyranose.^[26] RG-II is highly branched and very complex compound that may be crosslinked by borate diesters.^[27] The RG-II backbone is similar to homogalacturonan; however, it is decorated with complex side chains, including xylogalacturonan and apioagalacturonan.^[28] It is believed that these three polysaccharide domains can create a pectin network throughout the matrix and middle lamellae of the primary cell wall. This network has significant potential for its structure to be modulated by cell wall-based enzymes.^[22]

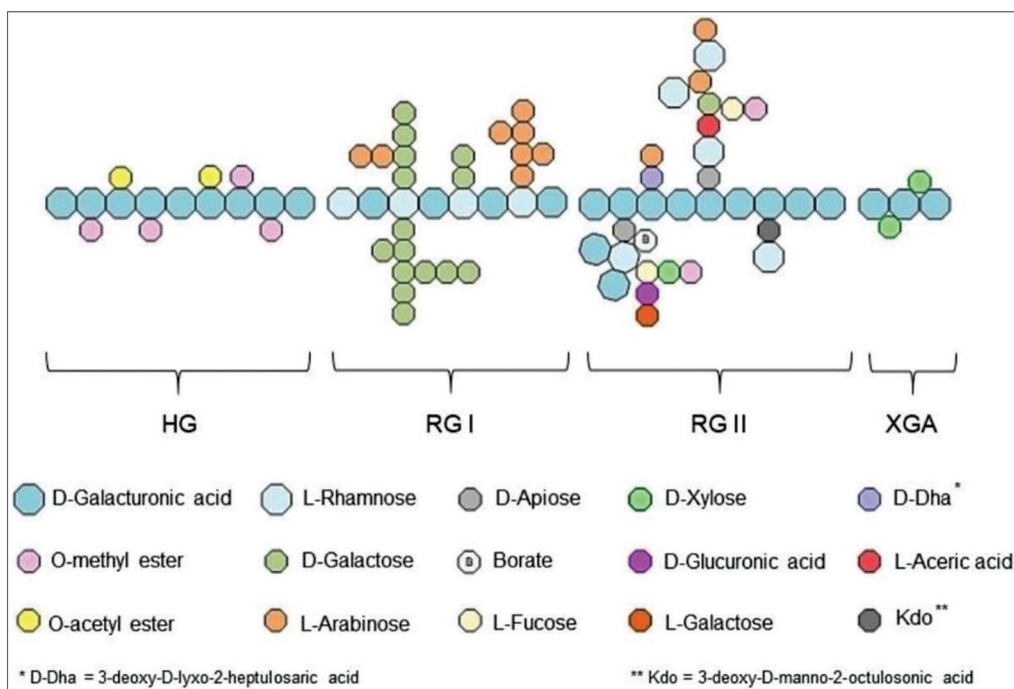


Figure 1: Chemical structure of the pectin molecule^[29]

The capabilities and abilities of pectin in different applications are determined by its chemical composition and structure. The capacity to gel is one of the most crucial qualities.^[30] Inter- and/or intrachain connections in which the development of the gel is aided by hydrogen bonds, hydrophobic contacts, and/or ionic link between distinct (OH) groups that are free, methylated, or amidated carboxyl groups. As a consequence of this, the solubility of pectin in aqueous media plays a crucial role. This solubility is regulated by the chemical composition and structure of the pectin, as well as the kind of counter ion, the ionic strength, the pH value, and the temperature.^[30] Pectins offer several benefits when used as food and medicinal additives: (1) Pectins are a good choice for use in drug delivery systems because they exhibit the necessary stability in acidic environments, even at higher temperatures. (2) Pectins are effective carriers for delivering bioactive chemicals because they have strong gel-forming properties when divalent cations are present. (3) Pectins are known for being nontoxic, widely accessible, and inexpensive to create. (4) Pectins can be used to administer medications orally, nasally, or vaginally, and many patients find them to be effective.^[31] Pectin has several medicinal benefits, including the ability to cure diabetes, gastroesophageal reflux disease, and constipation as well as to prevent cancers of the prostate and colon, and additionally helpful for the ulcerated mouth; it prevents poisoning.^[32]

THERAPEUTIC APPLICATIONS OF PECTINS

In the pharmaceutical industry, pectin has been used; pectin has a positive effect on blood cholesterol levels. According

to a thorough study, it has been reported to lower blood cholesterol in a range of patients and researchers, and subjects.^[33] To significantly lower cholesterol, a patient must consume at least 6 g of pectin daily. Pectin doses of less than 6 g per day are ineffective.^[34] As additions in food and medicinal formulations, pectins provide a number of benefits: (1) Pectins may form excellent gels when divalent cations are present, making them appropriate carriers for delivering bioactive compounds. They are frequently employed for delivering medications via the oral, nasal, and vaginal routes, and many patients find them to be effective.^[31] (2) Pectins have a long history of being thought of as nontoxic, readily available, and having minimal production costs. Antiobesity medications and eye therapies now have longer contact times because pectin can form gels in acidic media.^[35] Gels' tendency to swell in the acidic environments makes them useful in the treatment of obesity and weight loss. Before digestion, the gels expand and adhere to the stomach walls when they come into contact with the aqueous environment of gastric fluids, causing satiety and a lack of appetite.^[36] Additionally, meals high in soluble fiber, such as pectin, raise the excretion of bile acid and lower cholesterol, which reduces the risk of cardiovascular disease, and are associated with its capacity to lower cholesterol.^[37,38] According to studies, LM pectin does not lower cholesterol levels as efficiently as high molecular weight HM pectin.^[37] When pectin–lipase complexes are produced, competitive inhibition between the substrate (oil/fat) and the inhibitor (pectin) takes place. Pectin's moderate acidity prevents it from dissociating in the stomach environment and enables it to covalently bind to the active sites of pancreatic lipase.^[38]

POTENTIAL MECHANISMS OF PECTIN AS AN ANTIDIABETIC AGENT IN DIABETES MELLITUS TYPE 2

Pectin and guar gum are two examples of soluble dietary fibers that have been shown in a number of studies to lower blood sugar levels and/or insulin release after a sugar load has been administered. These benefits have been attributed to pectin and guar gum's ability to bind water and form a gel-like substance.^[39] Additionally, it has been hypothesized that the consumption of soluble fibers can improve glucose tolerance in healthy individuals by reducing the height of postprandial glycemia and/or guarding against late hypoglycemia. Both of these mechanisms are thought to be responsible for the beneficial effects of soluble fibers.^[40] As well as diabetes patients.^[41] Dietary fiber plays, in particular, a role in managing the risk of this chronic disease. Fiber-rich foods typically require more chewing time, which may promote sensory satiety and result in smaller meals.^[42] Additionally, fibers may slow intestinal passage rates, resulting in a more gradual absorption of nutrients and protracted sensations of fullness.^[43] By decreasing fatty acid and protein bioavailability, they may also reduce energy absorption.^[44] Finally, the fermentation of dietary fibers in the colon raises the content of short chain fatty acids, which may improve satiety through a variety of pathways.^[45] Pectin and guar gum are two examples of soluble dietary fibers that have been shown in a number of studies to reduce the amount of insulin released in response to a sugar load as well as lower blood glucose levels. In addition, it has been postulated that soluble fibers help diabetics and healthy individuals maintain normal blood sugar levels by lowering the peak of postprandial glycemia and/or preventing late hypoglycemia. This is one of the ways in which soluble fibers are thought to be beneficial.^[46,47] Pectin's effects on protein digestion and absorption, iron bioavailability, cholesterol absorption, bile acids, and other lipids, and utilization of beta-carotene are all influenced by its molecular weight as well as the level of esterification it undergoes. This has been demonstrated scientifically. Recent studies have shown that low-methoxyl pectin ferments more quickly than high-methoxyl pectin, both *in vivo* and *in vitro*. *In vivo* means in the body, and *in vitro* means in a test tube.^[47,48]

PERSPECTIVES AND CONCLUSIONS

Numerous clinical and scientific studies centered on the application of nanotechnology in the diagnosis monitoring and treatment of diseases. Diabetes mellitus is an example of this disease. A literature review was conducted, taking into account a database of articles from several reputable publications, with a particular emphasis on the application of pectin-modified nanomaterial in the improvement of T2DM. The use of nanotechnology in the treatment of diabetes is a potential strategy that needs to be thoroughly investigated. Improvements in glucose monitoring, insulin

delivery methods, and biomaterials research will all show to be crucial next steps in the improvement of treating diabetes. A master proposal included in this review aimed to study the impact of nanoparticles on the pancreatic enzymes in sera of T2DM patients by evaluating the lipase and amylase activities in sera of T2DM patients in the absence and presence of nanoparticles, evaluation of lipid profile, as well as ghrelin levels in sera of T2DM patients, and in the assessment of the relationship of pancreatic enzymes and studied biochemical parameters.

Ethical approval

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Conflicts of interest

There are no conflicts of interest.

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