Antidiabetic Agents: Biological Macromolecules

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ABSTRACT

Diabetes mellitus, which is characterised by persistent hyperglycaemia, is a huge issue to the health of people all over the world. In spite of their efficacy, conventional diabetes treatments can come with a number of undesirable side effects and restrictions. Research into alternative medicines, such as the investigation of biological macromolecules with antidiabetic effects, has been accelerated as a result of this. This review looks into this fascinating field, investigating the many classifications of macromolecules as well as the possible methods by which they exhibit their positive effects. There are many different kinds of biological macromolecules that have the potential to treat diabetes. Some of these macromolecules include polysaccharides, proteins, and bioactive lipids. Different parts of glucose metabolism are affected by each category, which each contains its own set of distinctive traits. Glucans generated from plants and chitosan are two examples of polysaccharides that have the ability to increase insulin sensitivity and delay the absorption of carbohydrates. Some proteins, including as insulin and glucagon-like peptide-1 (GLP-1), have the ability to directly influence the production of insulin and the absorption of glucose. Bioactive lipids, which include omega-3 fatty acids and phospholipids, have been shown to have anti-inflammatory and insulin-sensitizing effects via their presence.

This chapter highlights the potential of nanocarrier systems for the distribution of these macromolecules in a specialised manner and for improving their overall effectiveness. For the purpose of encapsulating and distributing these therapeutic compounds, some examples of platforms that show promise include hydrogels, polymeric nanoparticles, and liposomes. In conclusion, the evaluation emphasises the need of doing more research in order to guarantee the highest possible levels of safety, effectiveness, and cost-efficiency for these prospective

diabetes treatments. The research that are now being conducted into enhanced delivery methods, combination treatments, and personalised medicine approaches show a great deal of promise for the management of diabetes in the future.

Keywords: Biological macromolecules, Polysaccharides, Food-derived peptides, Medicinal plants, Diabetes mellitus, Anti-diabetic.

1. INTRODUCTION

Diabetes mellitus is a metabolic ailment that is characterised by hyperglycaemia, which is caused by abnormalities in insulin production, insulin action, or both. Diabetes mellitus is a chronic condition. Approximately 537 million persons aged 20-79 years were living with diabetes throughout the globe in 2021, as reported by the International Diabetes Federation (IDF), and it is anticipated that this figure would increase to 784 million by the year 2045. To preventing or delaying the development of complications such as cardiovascular disease, neuropathy, nephropathy, and retinopathy, the treatment of diabetes strives to establish glycaemic control [9]. Currently available treatment options include changes to one's lifestyle (such as diet and exercise), oral antidiabetic medicines (such as metformin, sulfonylureas, and DPP-4 inhibitors), injectable therapy (such as insulin and GLP-1 receptor agonists), and bariatric surgery. These therapies, on the other hand, have certain drawbacks, including the potential for side effects, hypoglycaemia, weight gain, and treatment failure over the course of time. Over the last several years, there has been a rising interest in investigating alternative treatment techniques for the management of diabetes [10]. One of these approaches include the utilisation of biological macromolecules. Large molecules that are not only necessary for a variety of biological processes but also display a wide range of forms and functions are referred to as biological macromolecules. The purpose of this paper is to offer an overview of the potential for biological macromolecules, such as proteins, peptides, polysaccharides, and nucleic acids, to act as anti-diabetic medicines. In this section, we will talk about the categorization of these diseases, the methods of action, the preclinical and clinical data, and the potential for future therapy of diabetes.

2. BIOLOGICAL MACROMOLECULES AS ANTIDIABETIC AGENTS:

A large variety of chemicals that are present in living organisms are included in the category of biological macromolecules. They are vital in the construction of cells, the transmission of signals, and the metabolism of cells. Because of their capacity to affect a variety of pathways that are involved in glucose homeostasis, insulin sensitivity, and pancreatic function, several different classes of biological macromolecules have shown that they have the potential to act as potential anti-diabetic medicines. Proteins, peptides, polysaccharides, and nucleic acids are all examples of these proteins.

2.1 Proteins

Amino acids are the building blocks of proteins, which are enormous, complicated structures that are held together by peptide bonds. Within the context of biological systems, they perform the functions of structural components, enzymes, hormones, and receptors. Insulin, glucagon-like peptide-1 (GLP-1), adiponectin, and insulin-like growth factor-1 (IGF-1) are some of the proteins that have been discovered as having the potential to exhibit anti-diabetic effects.

2.2 Insulin

In the pancreatic islets of Langerhans, the β-cells are responsible for the production of insulin, which is a peptide hormone. As a result of its ability to stimulate glucose uptake, glycogen synthesis, and lipogenesis in target tissues such the liver, muscle, and adipose tissue, it is an essential component in the maintenance of glucose homeostasis. Hyperglycaemia and diabetes mellitus are both conditions that may be caused by insulin insufficiency or insensitivity. One of the most important aspects of diabetes care for both type 1 and advanced type 2 diabetes is the use of exogenous insulin therapy. The creation of new insulin analogues that have enhanced pharmacokinetic and pharmacodynamic characteristics has been made possible by recent breakthroughs in the field of protein engineering and formulation technology. Both rapid-acting insulin analogues (such as insulin lispro and insulin aspart) and long-acting insulin analogues (such as insulin glargine and insulin detemir) are examples of these types of insulin analogues. These types of insulin analogues provide better ease and flexibility in insulin treatment. As an additional measure to improve patient adherence and quality of life, efforts are now being made to create insulin formulations that are accessible for oral administration as well as non-invasive insulin delivery methods [22,26].

2.2.1 Type 2 Diabetes and Insulin Secretion

Type 2 diabetes is characterized by impaired insulin secretion and function. This passage explores the possibility that plant-derived insulin-like proteins might offer a dietary approach to managing this condition [1].

2.2.2 Traditional Insulin Secretion Stimulants

The passage acknowledges the role of certain amino acids and whey proteins in stimulating insulin secretion. However, it highlights the limitations of these approaches, particularly the need for further research on their safety and efficacy in humans [20].

2.2.3 Plant-Based Insulin-Like Proteins

The focus then shifts to plant-based insulin-like proteins. Historical evidence suggests the presence of insulin-like activity in various plants like green beans and spinach. More recent research has isolated and characterized these proteins from Bauhinia variegata and Costus igneus leaves [20].

2.2.4 Properties of Plant-Based Insulin-Like Proteins

These plant-based proteins exhibit properties similar to mammalian insulin. They bind to insulin receptors, stimulate glucose uptake in adipocytes, and possess hypoglycemic effects in diabetic animal models. Interestingly, these proteins seem to be distinct from mammalian insulin in structure, which might explain their potential for oral administration.

2.2.5 Amylin

In the pancreas, the β-cells are responsible for the secretion of a hormone called amylin, which is a pancreatic peptide hormone. It does this via decreasing the release of glucagon,

delaying the emptying of the stomach, and inducing satiety, all of which work together to manage postprandial glucose levels. Several amylin analogues, including pramlintide, have been created with the purpose of treating diabetes of both type 1 and type 2 varieties. It has been shown that pramlintide, which is given subcutaneously prior to meals, may enhance glycemic control and lead to a reduction in body weight in diabetic individuals.

2.2.6 Leptin

The hormone leptin is a peptide that is released by adipocytes and has a significant role in the regulation of both the energy balance and the weight of the body. Through its action on the hypothalamus, it both reduces appetite and raises the amount of energy that is expended. There is a correlation between leptin shortage or resistance and obesity as well as insulin resistance, which highlights the probable role that leptin plays in the pathophysiology of diabetes. In animal models of diabetes, leptin replacement treatment has shown some degree of success; however, the extent to which it is effective in human patients has not yet been thoroughly determined [13].

2.2.7 Food-Derived Peptides

It has been observed that several bioactive peptides that are produced from dietary proteins have the ability to inhibit the progression of diabetes [4]. Possible mechanisms of action for these peptides include the inhibition of key enzymes involved in the metabolism of carbohydrates, the enhancement of insulin secretion or sensitivity, and the exertion of antioxidant and anti-inflammatory capabilities. Some examples of enzyme inhibitors are dipeptidyl peptidase-4 (DPP-4) inhibitors that are generated from dairy proteins, angiotensin-converting enzyme (ACE) inhibitors that are derived from fish proteins, and α-glucosidase inhibitors that are derived from grain proteins. Even though the clinical data that supports the anti-diabetic benefits of food-derived peptides is still in the process of developing, these peptides offer a potential field for further study and development in the future [25].

3. POLYSACCHARIDES

Complex carbohydrates are known as polysaccharides. Polysaccharides are made up of long chains of monosaccharide units that are connected by glycosidic linkages. They function as structural components in both plants and animals, and they are also involved in the storage of energy, the transmission of signals between cells, and the regulation of the immune system. Several polysaccharides derived from natural sources have been extensively researched for the possibility that they possess anti-diabetic characteristics [11].

3.1 Dietary polysaccharides

The term "dietary polysaccharides" refers to naturally occurring polysaccharides that may be consumed and are necessary for our day-to-day lives. Polysaccharides, which are often isolated from medicinal plants, grains, fruits, vegetables, edible mushrooms, and therapeutic foods, have garnered increased attention from researchers owing to the fact that they are low in toxicity and exhibit a wide variety of pharmacological activity. These molecules are made up of the monosaccharide unit and are connected to one another by glycosidic linkages. An important area of study that has recently come to the forefront is the evaluation of the effects of polysaccharides that possess anti-diabetic characteristics. Polysaccharides that have been

purified from pumpkin, sea cucumber, goji berry, mushroom, bean, tea, and oat have been shown to have beneficial effects on glucose homeostasis, to reduce the complications of diabetes through the protective mechanism against oxidative stress injury, and to eventually improve insulin sensitivity [16]. These findings have been presented in a number of different studies. Furthermore, dietary non-digestible polysaccharides that are produced from plants and foodstuff are recognised as powerful modulators of gut microbiota. These polysaccharides have the ability to support certain beneficial microorganisms that are found in the human gut. In addition, this has resulted in an increasing focus on the extraction of new bioactive polysaccharides and their use as functional components. These polysaccharides modify the microbiota in the gut, which in turn improves the healthy metabolism and overall health of the host. Therefore, polysaccharides are regarded to be prebiotic compounds, and there is a growing body of evidence suggesting that they may have beneficial benefits in the management of metabolic illnesses such as diabetes. We discuss the underlying molecular mechanisms that are related to oxidative stress and inflammatory factors, which could be supportive in alleviating type-2 diabetes [19]. In this comprehensive review, we summarise some of the most common dietary polysaccharides that are derived from medicinal plants, grains, fruits, vegetables, edible mushrooms, and medicinal foods. These polysaccharides have an impact on metabolic health.

3.2 Mechanism of Dietary Polysaccharides on Anti-Diabetic Activities

Polysaccharides are typically removed from dietary components by a variety of physiological, chemical, or enzymatic digestive processes. These therapies have been discovered to have the ability to reduce the risk of developing diabetes. In the previous research, it was shown that the ingestion of polysaccharides might ameliorate diabetes via mechanisms of action on gastrointestinal viscosity, gastrointestinal satiety, colon fermentation, and anti-gastrointestinal inflammation [2, 12]. In a similar vein, the purpose of the current research was to explore the many in vivo and in vitro experiments that have been conducted to determine the hypoglycemic, antioxidant, and anti-inflammatory effects that dietary polysaccharides have. It has been shown that dietary polysaccharides have the ability to increase the bulk of pancreatic β-cells, activate the PI3K/Akt pathway, and trigger insulin signalling pathways via insulin receptors. As a result of their ability to alter ERK/JNK/MAPK pathways, they provide relief from β-cell dysfunction [7].

3.3 Unveiling the Potential of Polysaccharides in Combating Type 2 Diabetes

Type 2 diabetes, characterized by chronic hyperglycemia (high blood sugar), is a growing global health concern. While conventional therapies exist, there is ongoing research for novel approaches to manage the condition effectively. This exploration delves into the potential of polysaccharides, a class of complex sugars, as dietary supplements for type 2 diabetes [5].

3.4 Combating Hyperglycemia and Hyperlipidemia

Impaired insulin function and glucose tolerance are hallmarks of type 2 diabetes. The study reveals that polysaccharides derived from various sources, including gum exudates, corn silk, and certain mushrooms, demonstrate promising hypoglycemic effects in animal models. These polysaccharides may work by mimicking insulin action or influencing glucose metabolism pathways.

Furthermore, the research highlights the hypolipidemic potential of polysaccharides. Studies suggest that polysaccharides can significantly reduce total cholesterol, triglycerides, and low-density lipoprotein (LDL) levels, often referred to as "bad cholesterol," while increasing beneficial high-density lipoprotein (HDL) levels. This ability to regulate blood lipids can contribute to a holistic approach to managing diabetes complications.

3.5 Harnessing Antioxidant Power

Chronic hyperglycemia in diabetes leads to the generation of excessive free radicals, which damage cells and tissues. This phenomenon, known as oxidative stress, plays a significant role in the progression of diabetes. The good news is that polysaccharides have been shown to exhibit antioxidant properties.

Several studies referenced in the passage demonstrate that polysaccharides can enhance the activity of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). These enzymes neutralize free radicals, protecting pancreatic beta cells from oxidative damage and potentially slowing the decline of insulin production.

3.6 Taming Inflammation: A Crucial Ally

Chronic, low-grade inflammation is another critical player in type 2 diabetes. Pro-inflammatory cytokines like interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α) contribute to insulin resistance and beta cell dysfunction. The research highlights the anti-inflammatory potential of polysaccharides.

Animal studies have shown that polysaccharides can reduce the production of these pro-inflammatory cytokines, thereby improving insulin sensitivity and protecting beta cells from damage. This suggests that polysaccharides may offer a valuable strategy to combat the inflammatory aspects of type 2 diabetes.

The passage provides a glimpse into various investigations exploring the benefits of polysaccharides. For instance, studies on polysaccharides extracted from Angelica sinensis roots and Rehmannia glutinosa roots demonstrate their ability to lower blood glucose levels and reduce inflammatory markers in diabetic mice. Similarly, polysaccharides from Morus alba L. fruit and Pleurotus sajor-caju mushrooms have been shown to decrease blood sugar and pro-inflammatory cytokine production in diabetic animals.

The research presented paints a promising picture for the potential role of polysaccharides in managing type 2 diabetes. Their ability to combat hyperglycemia, hyperlipidemia, oxidative stress, and inflammation suggests a multi-pronged approach to tackling this complex condition. However, it is important to note that the studies referenced primarily involve animal models. While they offer valuable insights, further clinical trials are needed to establish the safety and efficacy of polysaccharides in human populations [14].

4. B-GLUCANS

The polysaccharides known as β-glucans may be discovered in the cell walls of several organisms, including bacteria, fungus, yeasts, algae, lichens, and plants like oats and barley. Through the delay of glucose absorption in the gut, the enhancement of insulin sensitivity,

and the enhancement of pancreatic β-cell activity, it has been shown that these substances possess the ability to alleviate diabetes. Glycemic control and lipid metabolism in persons with type 2 diabetes have been shown to be improved with the use of dietary supplementation with β-glucans, as proven by clinical investigations.

5. POLYSACCHARIDES FROM MEDICINAL PLANTS

A wide variety of medicinal plants contain polysaccharides that have the ability to reduce the risk of developing diabetes. Polysaccharides isolated from plants such as Gymnema sylvestre, Momordica charantia (bitter melon), and Panax ginseng, for instance, have been shown to exhibit hypoglycemic effects. These effects are characterised by the enhancement of insulin production, the inhibition of glucose absorption, and the improvement of insulin sensitivity. An additional factor that contributes to the overall therapeutic efficiency of these polysaccharides is the possibility that they exhibit antioxidant and anti-inflammatory properties.

6. NUCLEIC ACIDS (NA)

In living organisms, nucleic acids, which include deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), serve as the genetic material. They also play important roles in the creation of proteins, the control of genes, and the transmission of signals between cells. Emerging data shows that nucleic acids may potentially have therapeutic promise in the treatment of diabetes. Although nucleic acids are largely recognised for their involvement in molecular biology and genetics, this is not everything that they are known for.

6.1 Functional Nucleic Acids

The harmful effects of diabetes mellitus (DM) on a variety of organs, including the skin, kidneys, eyes, and nerves, are well documented and acknowledged by the medical community. Hyperglycemia that is allowed to persist causes damage to the blood vessels throughout the body, which may result in metabolic disturbances and diabetic complications. These consequences are responsible for more patient deaths than diabetes itself. According to the figures that were compiled on the prevalence of these complications in diabetic patients, diabetic wounds (DW) accounted for 42 percent, diabetic nephropathy 21.8%, metabolic syndrome 20–25%, diabetic retinopathy 3.4–12.3%, and diabetic neuropathy 23 percent [17]. Diabetes-related problems continue to place a significant burden on both the health of patients and the economy, despite the availability of diagnostic tools and the ongoing development of treatment options [3]. On the other hand, other treatments such as gene therapy and induced b-cell regeneration have not been widely implemented to manage diabetes. Traditional general systemic and local treatments concentrate on insulin secretion and insulin sensitization, both of which can cause patients to experience unwanted side effects and lead to noncompliance with treatment as well as treatment failure. In the treatment of diabetes and its consequences, recent developments in therapy targets and innovative functional nucleic acid materials have brought forth fresh hope. The phrase "functional nucleic acid" refers to a broad category that encompasses nucleic acids and nucleic acid analogue molecules. This category encompasses a wide range of nucleic acids, including DNAzymes, aptamers, DNA tiles, and DNA origami, as well as unusual forms of nucleic acids. In recent years, the research has significantly advanced [24].

6.2 Functional Nucleic Acids for Diabetic Complications

Functional nucleic acids are a promising new class of therapeutics for diabetic complications. These molecules target various pathways involved in the development and progression of diabetic wounds (DFUs), nephropathy (DNep), and retinopathy [6,15].

6.2.1 Diabetic Foot Ulcers (DFUs)

- **Challenges:** DFUs are prone to infections and often lead to amputations. Current therapies have limited efficacy.
- **Promise of Functional Nucleic Acids**
  - tFNAs activate pathways promoting wound healing and reduce oxidative stress.
  - siRNA can target genes involved in inflammation and impaired healing.

6.2.2 Diabetic Nephropathy (DNep)

- **Causes:** Characterized by proteinuria, reduced kidney function, and high blood pressure.
- **Functional Nucleic Acids for DNep**
  - LNA-anti-miR-192 inhibits proteinuria and reduces fibrosis.
  - miR-10a/b targets TGF-β signaling to suppress fibrosis.
  - CHOP-ASOs protect kidney cells from damage.

6.2.3 Diabetic Retinopathy

- **Causes:** A microvascular complication leading to vision loss.
- **Functional Nucleic Acids for Diabetic Retinopathy**
  - tFNAs protect retinal cells from damage and improve insulin sensitivity.
  - tFNA-delivered resveratrol enhances the effects of tFNA on insulin resistance.
  - miR-200 nanoparticles inhibit angiogenesis.
  - GLUT1 siRNA reduces retinal glucose levels and protects retinal cells.
  - siRNA nanoparticles may be used for treatment and monitoring angiogenesis [27].

7. ANTISENSE OLIGONUCLEOTIDES (ASO'S)

RNA-specific oligonucleotides (ASOs) are nucleic acids that are short and single-stranded. They are intended to precisely bind to complementary messenger RNA (mRNA) sequences, which inhibits gene expression. Based on the results of preclinical research, it has been shown that ASOs that target genes that are involved in insulin resistance, inflammation, and β-cell dysfunction have shown promising results in the treatment of type 2 diabetes. In animal models of diabetes, for instance, it has been shown that ASOs that target hepatic gluconeogenic enzymes may enhance glucose metabolism and insulin sensitivity [23].

7.1 Small Interfering RNAs (siRNAs)

siRNAs are molecules of double-stranded RNA that have the ability to silence gene expression by either blocking translation or causing the breakdown of messenger RNA (mRNA). The therapeutic potential of small interfering RNAs (siRNAs) targeting genes that are involved in insulin signalling pathways, lipid metabolism, and inflammation has been

proven in preclinical models of type 2 diabetes [18]. The transport of siRNAs using nanoparticle-based carriers shows promise as a means of addressing the problems associated with the low stability and delivery efficiency of siRNAs [8]. In animal models, preclinical investigations have shown evidence that small interfering RNAs (siRNAs) targeting genes implicated in insulin resistance, inflammation, and β-cell dysfunction have the potential to enhance glucose metabolism and alleviate problems connected to diabetes [21].

7.2 Aptamers

Aptamers are nucleic acids that are short and single-stranded, and they have the ability to attach to certain target molecules with a high number of specificity and affinity. They are produced by a method known as Systematic Evolution of Ligands by Exponential Enrichment (SELEX), and they have been investigated for a variety of medicinal uses, one of which being diabetes. Aptamers that target important proteins involved in glucose homeostasis, such as insulin, insulin receptor, and glucose transporter, have shown the potential to be used as new anti-diabetic medicines [28]. These aptamers have the ability to control insulin signalling, glucose absorption, and the activity of pancreatic β-cells, providing a tailored strategy for the treatment of diabetic complications.

8. SUMMERY

Diabetes mellitus, a chronic metabolic disorder marked by hyperglycemia due to irregularities in insulin production or function, affected approximately 537 million adults globally in 2021, with predictions rising to 784 million by 2045. Achieving glycaemic control to prevent complications like cardiovascular disease, neuropathy, nephropathy, and retinopathy remains a primary goal in diabetes management. Current treatments, including lifestyle modifications, oral medications, injectable therapies, and bariatric surgery, often face limitations such as side effects, hypoglycemia, weight gain, and treatment failure over time. Consequently, there has been growing interest in alternative treatments, including biological macromolecules, which play crucial roles in biological processes and offer potential as antidiabetic agents. Proteins such as insulin, GLP-1, adiponectin, and IGF-1 exhibit significant antidiabetic effects. Advances in protein engineering have led to new insulin analogues, enhancing treatment flexibility and adherence. Plant-based insulin-like proteins are also promising due to their unique structures that may allow oral administration. Peptide hormones like amylin and leptin, as well as bioactive peptides derived from dietary proteins, have shown potential in regulating glucose levels and improving insulin sensitivity. Polysaccharides, complex carbohydrates from natural sources like pumpkin, sea cucumber, and medicinal plants, exhibit antidiabetic properties by improving glucose homeostasis and insulin sensitivity while acting as prebiotics that modulate gut microbiota. β-Glucans, found in the cell walls of various organisms, improve glycemic control and lipid metabolism in type 2 diabetes by delaying glucose absorption, enhancing insulin sensitivity, and boosting pancreatic β-cell activity. Additionally, nucleic acids, including DNA and RNA, have emerged as potential therapeutics in diabetes management. Functional nucleic acids such as DNAzymes, aptamers, and other analogues show promise in addressing diabetic complications like wounds, nephropathy, and retinopathy by promoting wound healing, reducing oxidative stress, and protecting cells from damage. Antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) demonstrate potential in targeting genes involved in insulin resistance, inflammation, and β-cell dysfunction, thereby improving glucose metabolism and insulin sensitivity. Aptamers, which are short, single-stranded

nucleic acids with high specificity and affinity for target molecules, offer a tailored approach to diabetes treatment by targeting proteins involved in glucose homeostasis, such as insulin and glucose transporter. This overview underscores the potential of biological macromolecules in developing novel antidiabetic therapies, providing a promising avenue for future research and treatment strategies

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