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Review article

Potential of biological macromolecules as innovative approach for diabetes management: A review

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Abstract

Diabetes mellitus, a complex and widespread metabolic disorder, presents a significant challenge to global health. While insulin therapy remains a cornerstone of treatment, its limitations, including therapeutic resistance and the development of associated complications, necessitate the exploration of innovative therapeutic strategies. This review delves into the promising realm of biological macromolecules, highlighting their potential to revolutionize diabetes management. We examine the diverse therapeutic applications of enzymes, growth factors, antibodies, polysaccharides, nucleic acids, and stem cells, elucidating their multifaceted roles in addressing the complex pathophysiology of diabetes. These macromolecules exert their therapeutic effects through intricate mechanisms, including precise modulation of glucose homeostasis, robust protection of insulin-producing beta cells, and effective attenuation of oxidative stress, a key driver of diabetic complications. A deep understanding of the metabolic pathways influenced by these molecules is crucial for optimizing their therapeutic efficacy and minimizing potential side effects. Recent advancements in protein engineering, targeted drug delivery systems, and regenerative medicine have paved the way for the development of highly specific, potent, and long-lasting biological macromolecular therapeutics. This review underscores the immense potential of biological macromolecules to transform diabetes care, emphasizing the critical need for continued research and clinical trials to translate these promising findings into clinically effective, patient-centered treatments.

1. Introduction

More than half a billion people are living with diabetes worldwide, affecting men, women, and children of all ages in every country, and that number is projected to more than double to 1.3billion people in the next 30 years, with every country seeing an increase in number of diabetes [1] arises from disrupts insulin secretion and/or action, leading to chronic hyperglycemia and a cascade of debilitating complications [2-4]. While conventional therapies like insulin and oral hypoglycemic agents remain indispensable for glycemic control, their limitations, including hypoglycemia risk, weight gain, and potential side effects, necessitate the continuous exploration of novel therapeutic avenues [5]. In this context, the emergence of biological macromolecules, a diverse class of complex molecules endowed with specific biological functions, has ignited a paradigm shift in the diabetes therapeutic landscape [6]. These macromolecules offer a tantalizing glimpse into the future of personalized medicine, characterized by targeted action on specific pathways, sustained therapeutic effects, and the potential to overcome the limitations of conventional therapies [7]. This comprehensive review delves deep into

the multifaceted potential of biological macromolecules in diabetes management. We will dissect their diverse classes, ranging from enzymes and growth factors to antioxidants and designer proteins, each wielding unique therapeutic weapons against the diabetic beast. We will unravel their intricate molecular mechanisms, demystifying the pathways they target and the cellular processes they modulate. Furthermore, we will illuminate the cutting-edge advancements in this field, from the development of biocompatible delivery systems to the engineering of designer proteins with enhanced efficacy and specificity. This journey into the world of biological macromolecules promises to unveil a new era in diabetes management. By harnessing the power of these nature-crafted tools, we may one day rewrite the narrative of this chronic disease, transforming it from a relentless foe into a manageable adversary.

2. Classes of Biological Macromolecules for Diabetes Management

A wide range of complex biological molecules are being investigated for their potential to treat diabetes. We will examine key examples of these molecules based on their natural origins.

2.1 Glucagon like peptide-1 (GLP-1) Receptor Agonists

These molecules can be conceptualized as master keys that unlock the full therapeutic potential of native GLP-1, an incretin hormone naturally synthesized by L-cells within the intestinal epithelium. Semaglutide; it is a synthetic version of the hormone GLP-1, naturally produced in the human body and released by the small intestine, Figure 1. Liraglutide; a fragment of the naturally occurring human GLP-1 sequence position 7-37, Figure 2, 3. Exenatide; it is a 39-amino acid peptide amide that's a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster. Exenatide is also known as a GLP-1 analog, Figure 4, 5. And Dulaglutide; also known as Trulicity, is a recombinant DNA-produced polypeptide analogue of human GLP-1. It's a disulfide-bonded homodimer fusion peptide that's 90% homologous to native GLP-1, Figure 6. GLP-1 receptor agonists are a class of medications designed to mimic the actions of the naturally occurring hormone, glucagon-like peptide-1 (GLP-1). By binding specific receptors on pancreatic beta cells, these macromolecules stimulate insulin secretion, suppress glucagon release, and slow gastric emptying. These combined effects contribute to improved blood glucose control and weight management [8, 9].

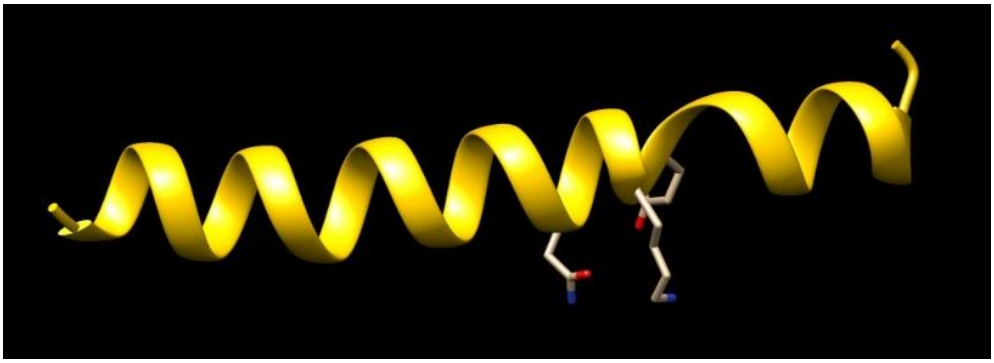

Figure 1. Semaglutide (PDB ID:7KI0).

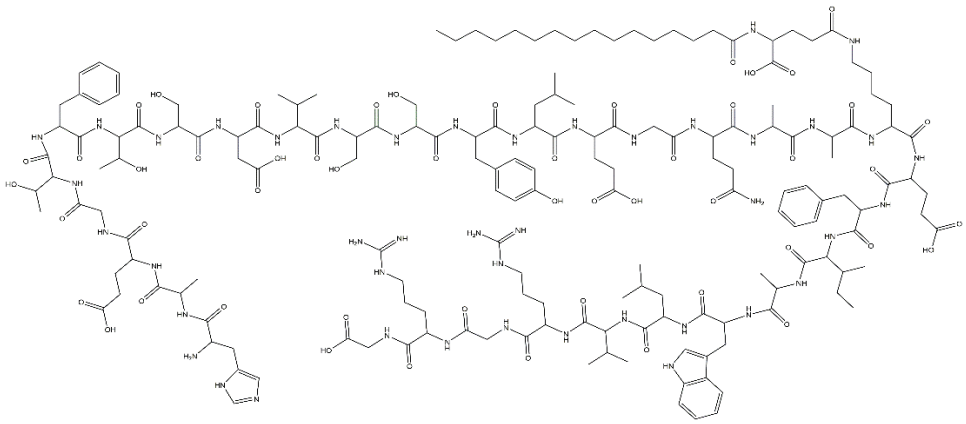

Figure 2. Liraglutide.

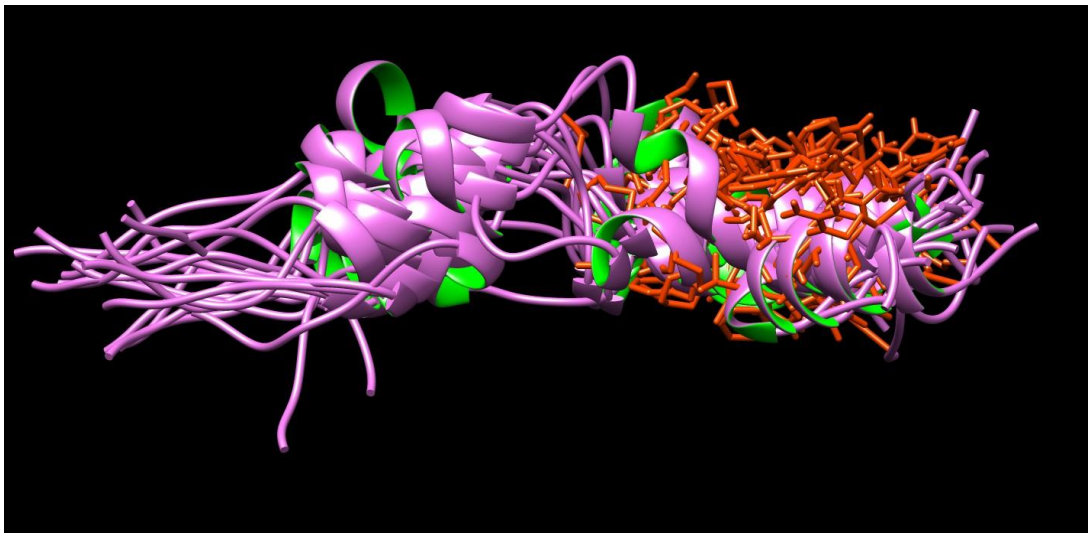

Figure 3. Liraglutide (PDB ID:4APD).

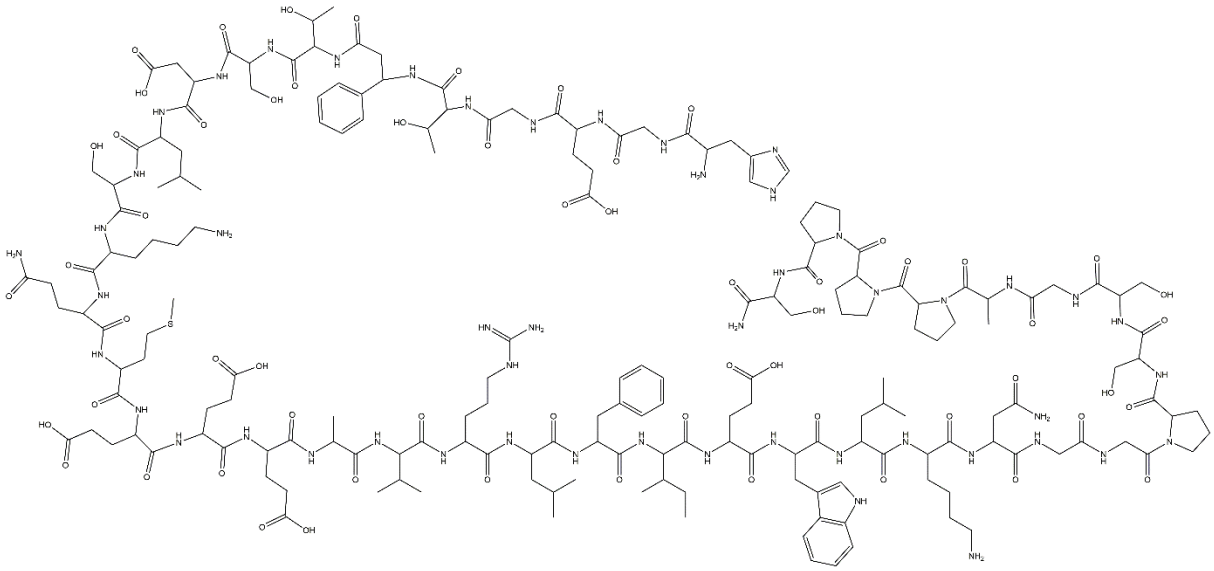

Figure 4. Exenatide.

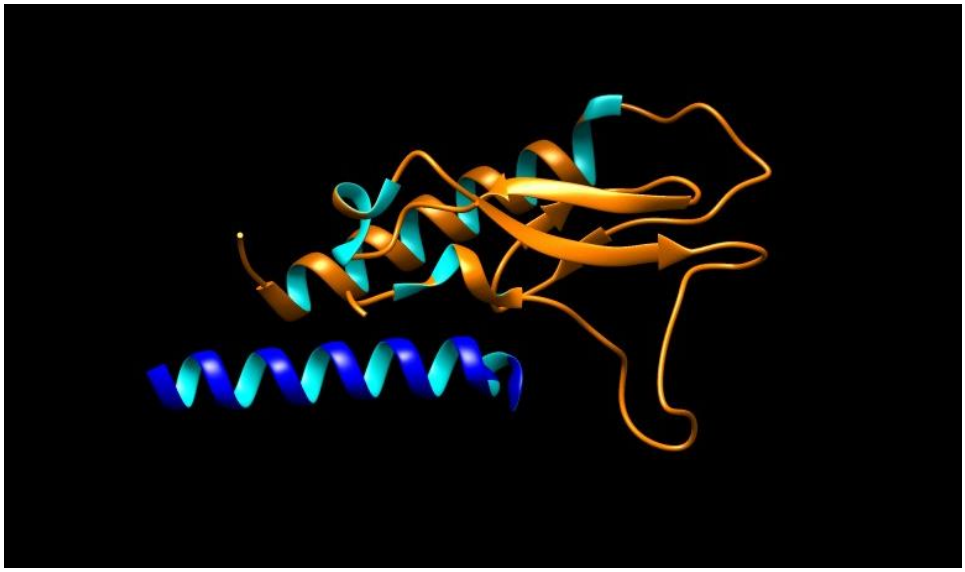

Figure 5. Exenatide (PDB ID:3C5T).

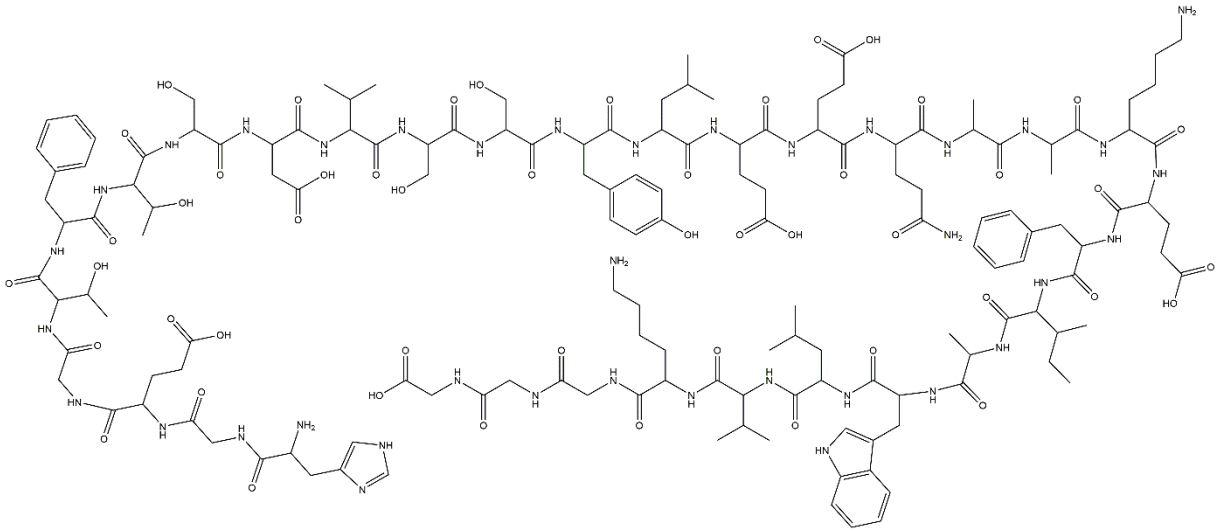

Figure 6. Dulaglutide.

Beneficial effects of GLP-1

Increased insulin production: Considering insulin as the body's key to unlocking glucose uptake in cells. GLP-1 agonists act like an additional support; by stimulating insulin production, researchers aim to enhance the beta cells' capacity to generate this vital hormone. Efforts to boost insulin output and accelerate its release are central to developing effective treatments for diabetes.

Decreased glucagon levels: Glucagon functions as an antagonistic hormone, stimulating hepatic glucose release. In contrast, GLP-1 agonists exert their influence by binding to specific receptors, thereby inhibiting the action of glucagon and consequently reducing hepatic glucose output.

Delayed gastric emptying: This coordinated action effectively decelerates the rate at which glucose enters the bloodstream. This provides the body with ample time to efficiently utilize available glucose stores. Consequently, glycemic control is enhanced, resulting in blood sugar levels that are closer to the desired range [10,11].

2.2 DPP – 4 Inhibitors

DPP-4 inhibitors function as defensive agents, safeguarding the integrity of the GLP-1 hormone. By preventing the DPP-4 enzyme from cleaving and inactivating GLP-1, these inhibitors effectively prolong the lifespan of this crucial incretin hormone. This extended circulation time allows GLP-1 to exert its glucose-lowering effects more potently and persistently. DPP-4 inhibitors, like Sitagliptin; it is a triazolopyrazine that exhibits hypoglycemic activity. It has a role as a serine proteinase inhibitor, a hypoglycemic agent, an EC 3.4. 14.5 (dipeptidyl peptidase IV) inhibitor, an environmental contaminant and a xenobiotic. It is a triazolopyrazine and a trifluorobenzene, Figure 7. Vildagliptin; it is a cyanopyrrolidine based drug. It is an oral inhibitor of DPP-4 enzyme. By preventing the inactivation of these hormones, vildagliptin increases insulin secretion and decreases glucagon release by the pancreas and is used to treat type 2 diabetes mellitus, Figure 8. And Linagliptin; it is a synthetic compound and is a DPP-4 inhibitor, phase III clinical study showed the drug can effectively reduce blood sugar, Figure 9. By inhibiting the breakdown of GLP-1, DPP-4 inhibitors indirectly enhance the hormone's activity. This strategy extends the lifespan of GLP-1, allowing it to exert its glucose-lowering effects for a longer duration. Consequently, these inhibitors offer similar glycemic benefits to GLP-1 receptor agonists, albeit through a different mechanism of action [12,13].

2.3 Growth Factors

Derived from a variety of sources including mesenchymal stem cells and platelets, these cellular factors exert a regenerative influence on pancreatic beta cells, stimulating their growth, repair, and survival. Examples include Fibroblast growth factors (FGFs, Figure 10) and hepatocyte growth factor (HGF, Figure 22). These macromolecules are emerging as potential players in diabetes management. FGFs, a family of proteins with diverse functions, have shown promise in improving insulin sensitivity, reducing liver glucose production, and potentially aiding weight loss. HGF, primarily known for its role in liver regeneration, also demonstrates potential benefits in diabetes by enhancing insulin sensitivity, exerting anti-inflammatory effects, and potentially safeguarding pancreatic beta cells. FGF further subdivided into FGF 1-23, Figure 11 – 21. By nurturing these vulnerable cells, growth factors aim to boost insulin production and potentially even regenerate damaged beta cells, offering a long-term solution to diabetes. While research is encouraging, further investigation is necessary to fully understand the therapeutic potential of these growth factors in diabetes treatment [14-16].

2.4 Antibodies

While antibodies are crucial for understanding the underlying cause of type 1 diabetes, there are currently no antibody-based treatments available to prevent or reverse the autoimmune process. However, research continues to

explore potential therapeutic applications of antibodies in diabetes management.

Monoclonal Antibodies: these are engineered proteins designed to precisely target specific molecules involved in the complex interplay of diabetes. By binding to these molecules, they can modulate their activity, offering a targeted approach to diabetes management. One notable example is Lixisenatide, a drug that belongs to the class of GLP-1 receptor agonists. It works by attaching itself to the GLP-1 receptor, amplifying the actions of this naturally occurring hormone. This enhanced signalling leads to increased insulin secretion, reduced glucagon release, and slowed gastric emptying, collectively contributing to improved blood sugar control, Figure 23 [17].

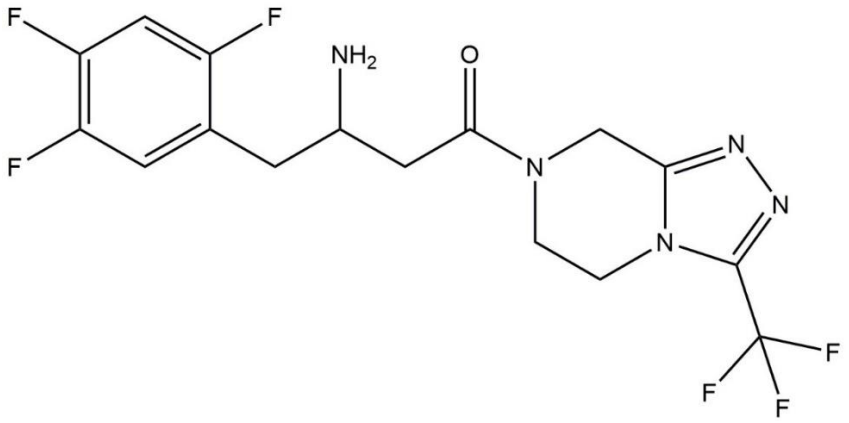

Figure 7. Sitagliptin.

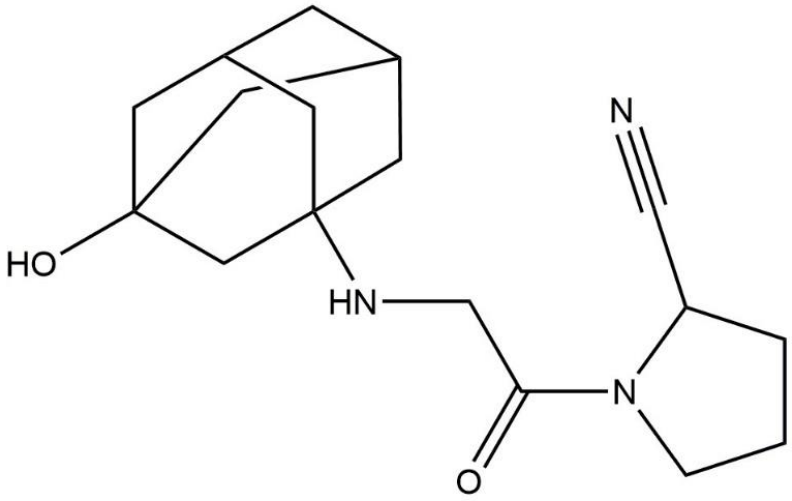

Figure 8. Vildagliptin.

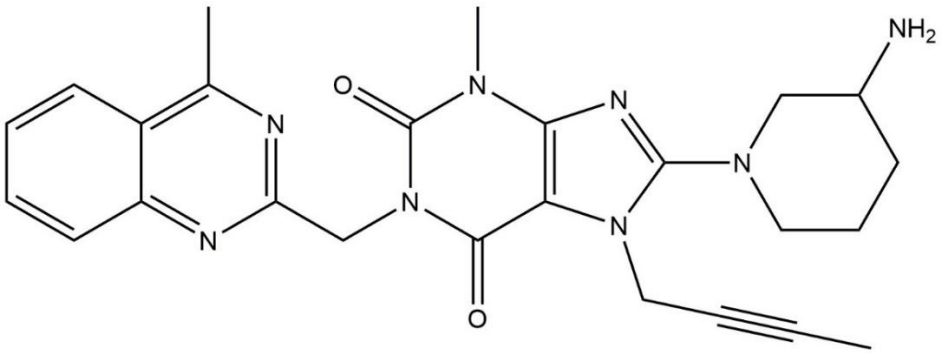

Figure 9. Linagliptin.

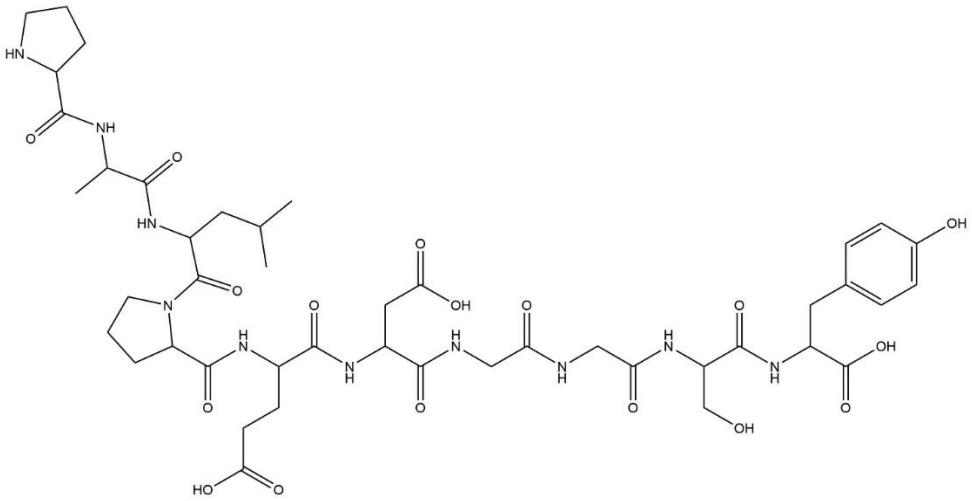

Figure 10. Fibroblast growth factor (FGF 1-10).

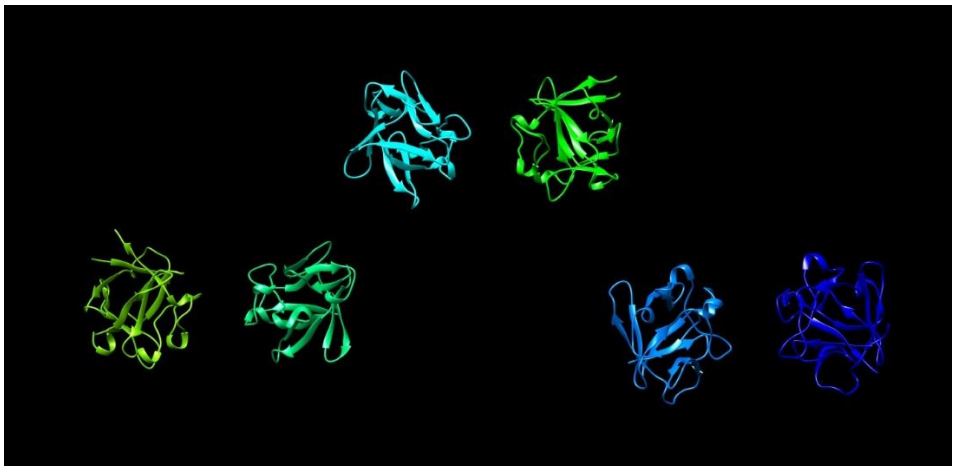

Figure 11. FGF1 (PDB ID:1AXM).

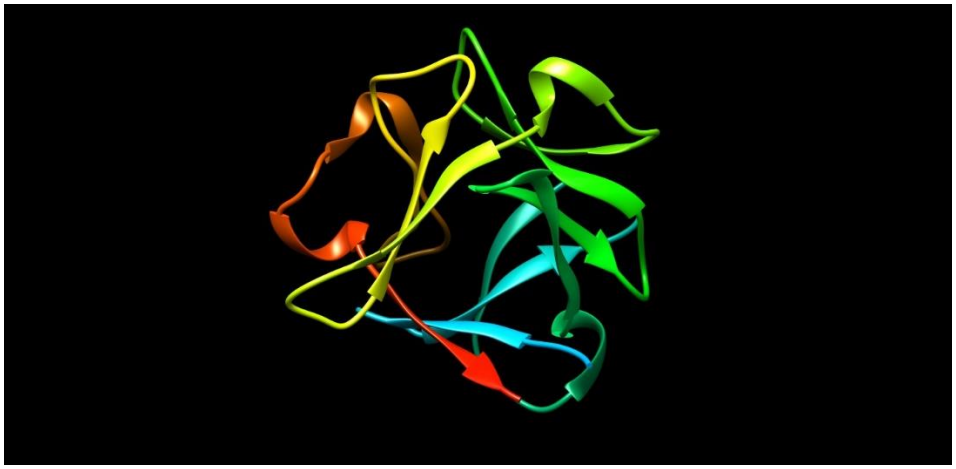

Figure 12. FGF2 (PDB ID:1BAS).

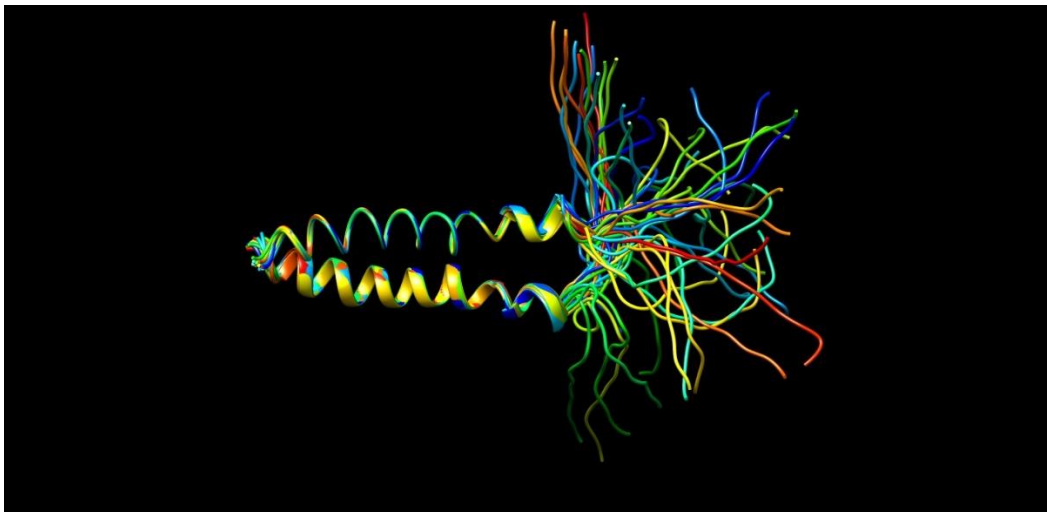

Figure 13. FGF3 (PDB ID:2LZL).

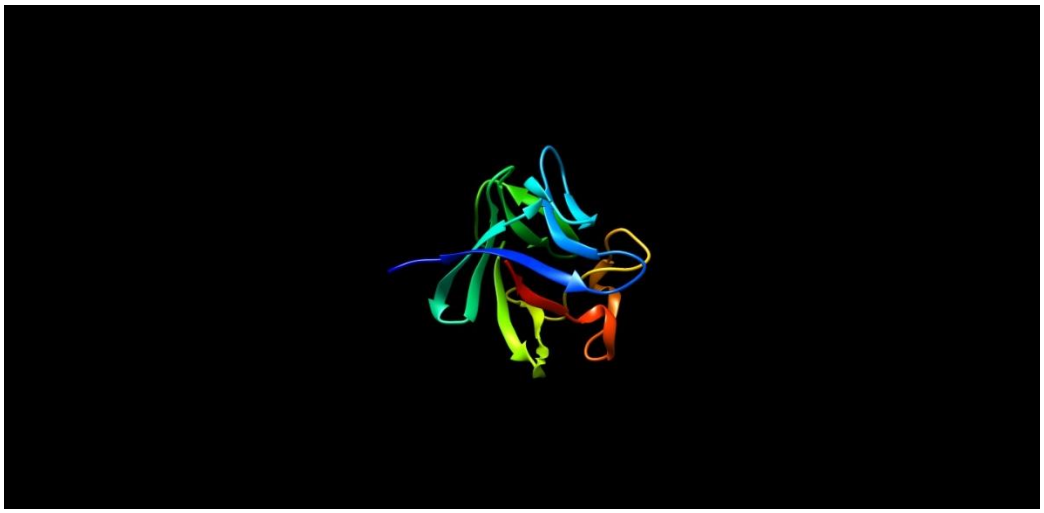

Figure 14. FGF4 (PDB ID:1IJT).

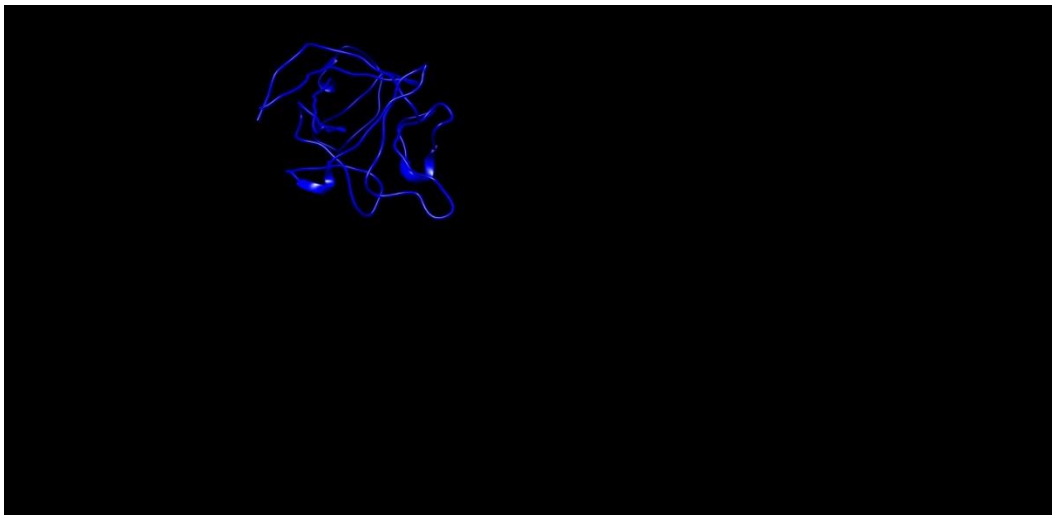

Figure 15. FGF12 (PDB ID:4JQ0).

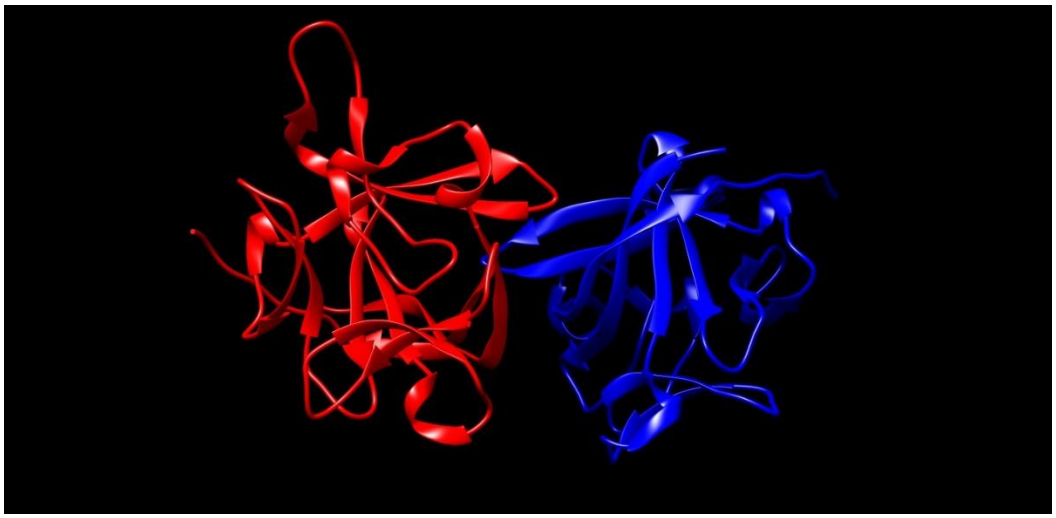

Figure 16. FGF13 (PDB ID:3HBW).

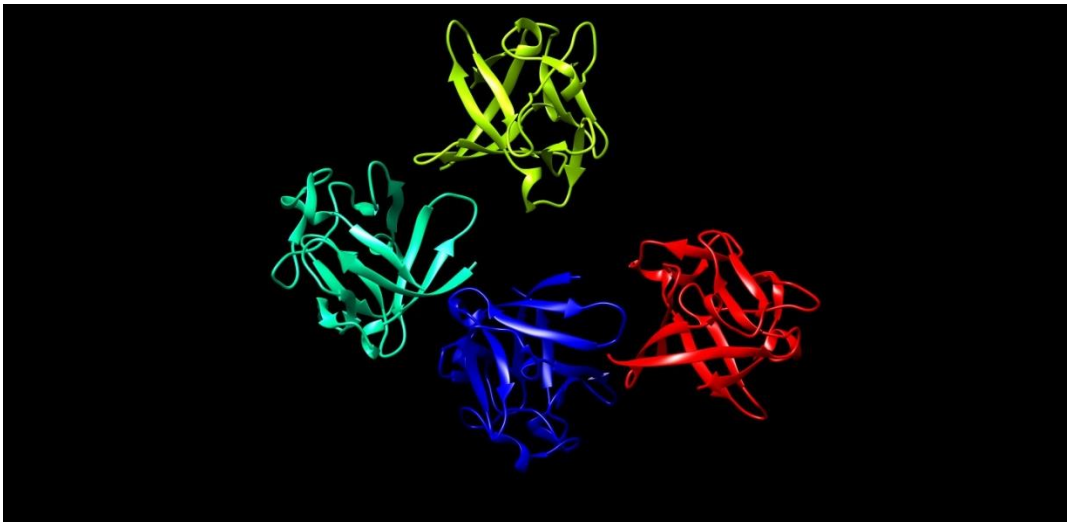

Figure 17. FGF18 (PDB ID:4CJM).

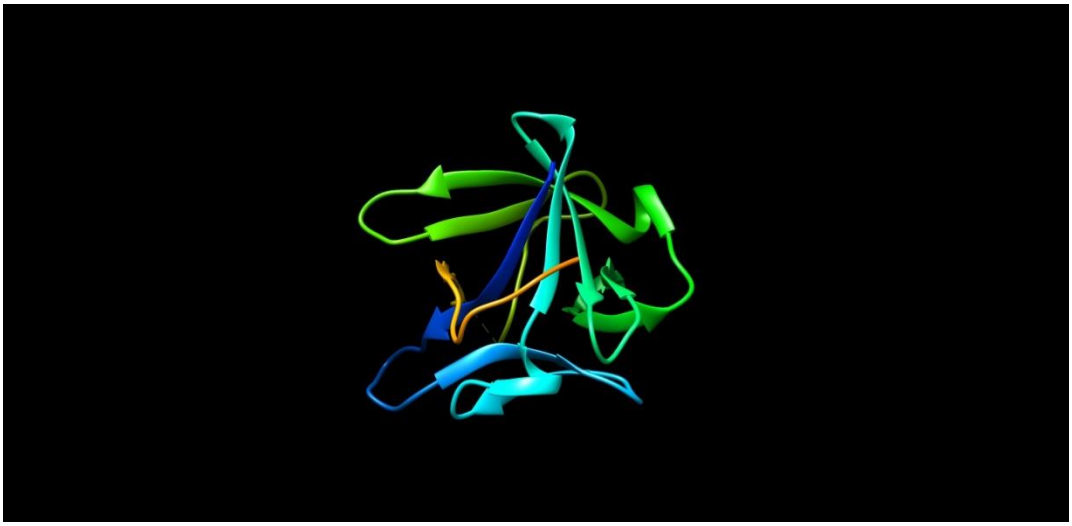

Figure 18. FGF19 (PDB ID:1PWA).

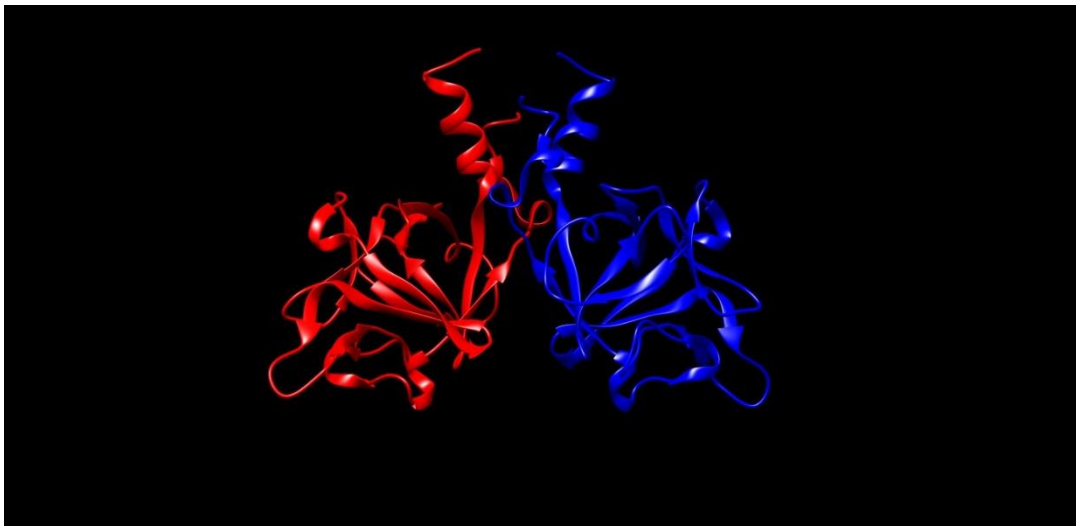

Figure 19. FGF20 (PDB ID:3F1R)

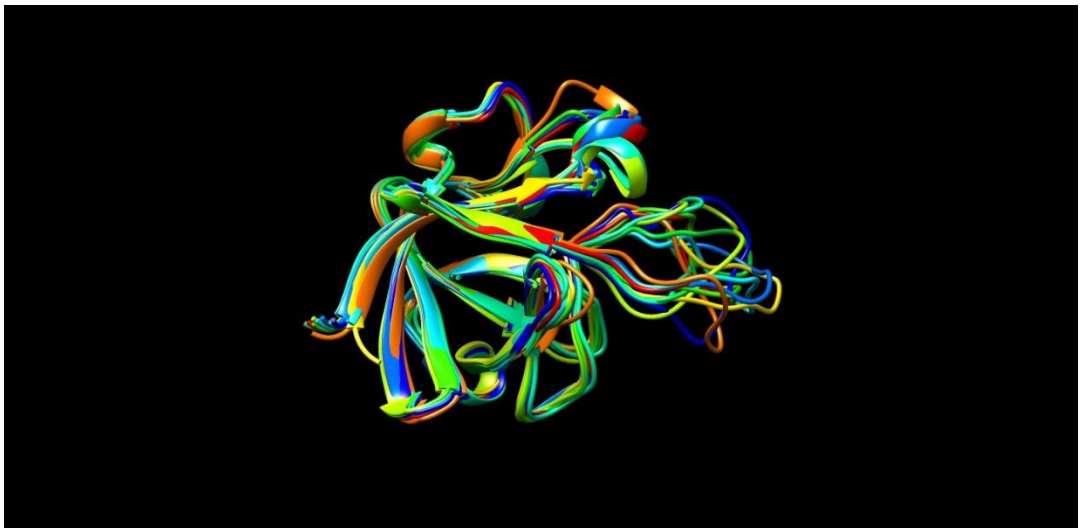

Figure 20. FGF21 (PDB ID:6M6E)

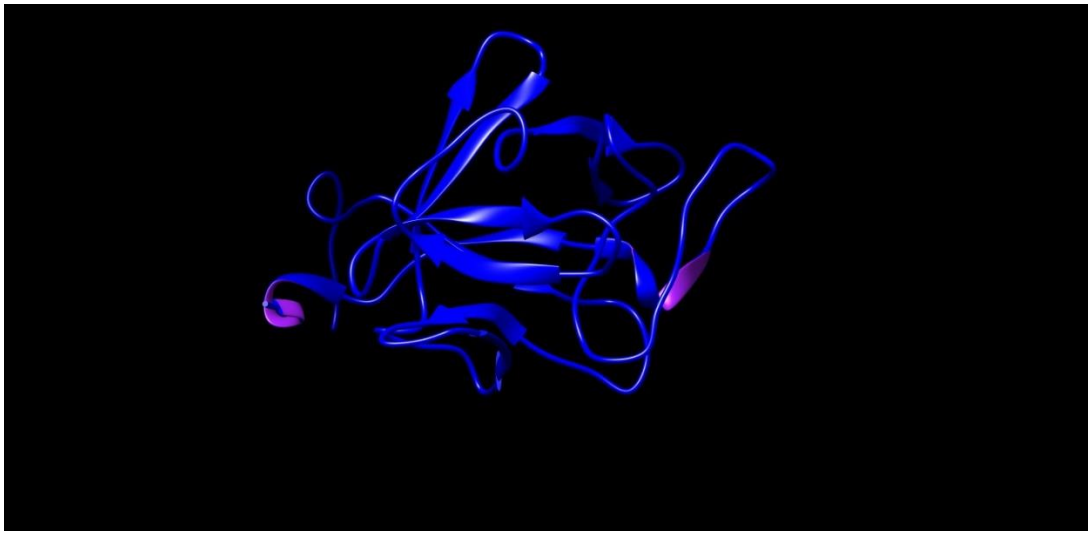

Figure 21. FGF23 (PDB ID:2P39)

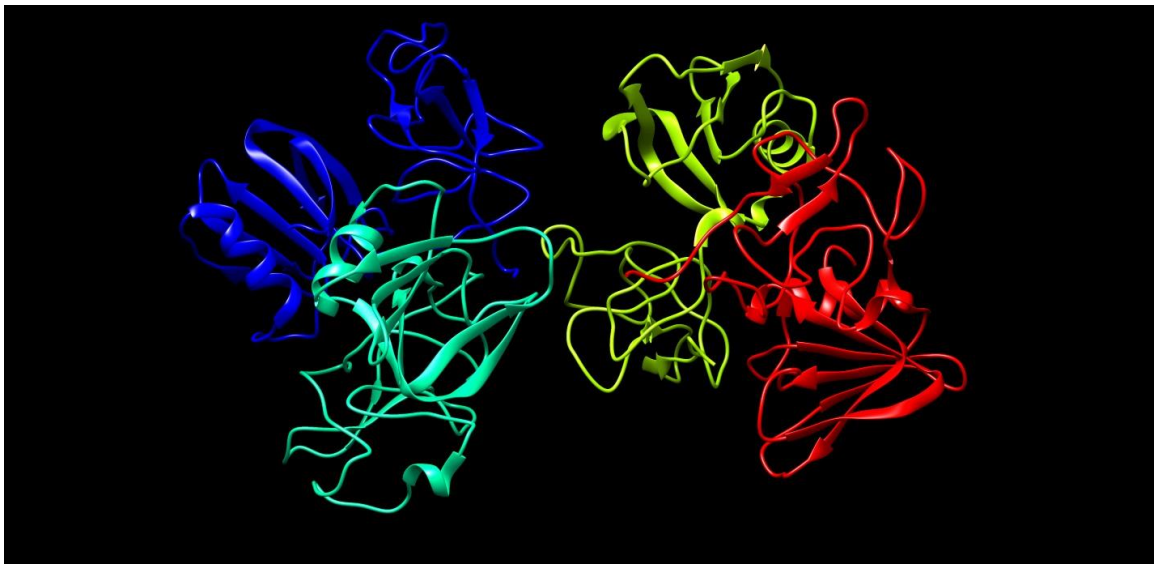

Figure 22. Hepatocyte growth factor (PDB ID:1GP9).

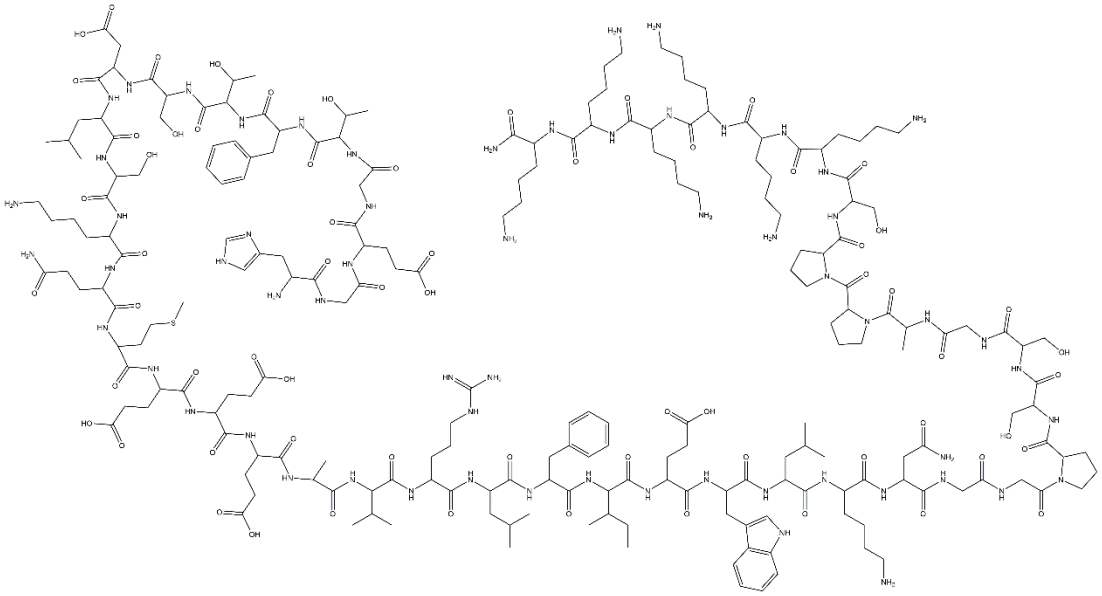

Figure 23. Lixisenatide.

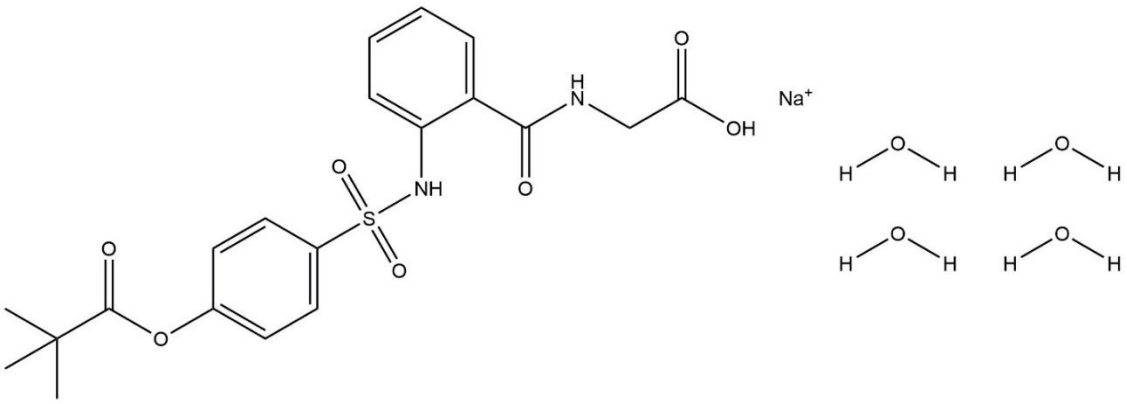

Figure 24. Adalimumab.

Anti-TNF-alpha antibodies: Anti-TNF-alpha antibodies, such as Adalimumab, have emerged as potential therapeutic agents in the management of type 2 diabetes. These antibodies target and neutralize tumor necrosis factor-alpha (TNF-alpha), a key inflammatory molecule implicated in the development of insulin resistance. By blocking the actions of TNF-alpha, these antibodies help to reduce inflammation and improve insulin sensitivity, thereby contributing to better blood sugar control, Figure 24 [18].

2.5 Nucleic Acids

While primarily known for their role in genetic information storage and transfer, nucleic acids are emerging as promising therapeutic agents in diabetes management.

Antisense Oligonucleotides: These molecules can specifically target and inhibit the production of certain proteins involved in diabetes pathogenesis. For instance, they can be used to reduce the levels of harmful proteins or increase the levels of beneficial ones [19]**.**

Small Interfering RNA (siRNA): Like **antisense oligonucleotides**, siRNA can silence specific genes involved in diabetes, offering a potential therapeutic approach. These short RNA molecules silence the expression of specific genes involved in glucagon production and glucose metabolism [19,20]. By targeting genes like glucagon or glucose-6-phosphatase, siRNAs offer potential for long-term glycemic control by directly disrupting their expression and function [21].

Gene Therapy: By introducing corrective genes into cells, gene therapy aims to restore normal function in diabetes. Vectors like Adeno-associated viruses (AAVs) are being explored to deliver functional insulin genes directly to pancreatic beta cells. This holds the potential for regenerating dysfunctional beta cells and restoring insulin production in individuals with diabetes [22,23]. While still in its early stages, this approach holds promise for treating genetic forms of diabetes.

2.6 Polysaccharides

Polysaccharides, complex carbohydrates composed of multiple sugar units, offer potential benefits in diabetes management. These natural compounds can help regulate blood sugar levels by slowing glucose absorption, improving insulin sensitivity, and promoting gut health. Additionally, some polysaccharides possess anti-inflammatory properties, which may be beneficial in managing diabetes-related complications. For example, Beta-glucans, a type of dietary fiber abundantly found in oats and other plant-based foods, have demonstrated potential benefits in managing blood sugar levels**.** These complex carbohydrates have shown promise in enhancing insulin sensitivity and improving overall glycemic control. By influencing factors such as glucose absorption and gut microbiota, beta-glucans contribute to a healthier metabolic profile [24]. Their ability to activate immune cells and modulate gut microbiota contributes to improved glucose uptake by peripheral tissues and reduced postprandial glycemic excursions [25].

2.7 Stem Cells

Their unique ability to transform into various cell types holds potential for regenerating insulin-producing cells, crucial for Type 1 diabetes. Additionally, stem cells can modulate the immune system and enhance insulin sensitivity. While challenges such as ethical considerations, tumor formation, and long-term efficacy persist, ongoing research is paving the way for potential breakthroughs in diabetes management. For example, Mesenchymal Stem Cells (MSCs); these multipotent stem cells hold significant potential for regenerating pancreatic beta cells, providing a potential curative approach for diabetes [26,27]. Preclinical studies demonstrate the ability of MSCs to differentiate into insulin-producing cells or stimulate the regeneration of existing beta cells, offering a promising avenue for future therapy [28].

3. Molecular Mechanisms and Targeted Pathways

Anti- Tumor necrosis factor-alpha (TNF-alpha) antibodies: TNF-alpha is a key inflammatory cytokine implicated in the development of insulin resistance. By inhibiting the body's ability to effectively utilize insulin, TNF-alpha contributes to elevated blood sugar levels. Consequently, neutralizing TNF-alpha can be a therapeutic strategy to enhance insulin sensitivity. By blocking the actions of this pro-inflammatory molecule, it is possible to improve glucose uptake in peripheral tissues such as muscle and fat, ultimately leading to a reduction in hyperglycemia [29,30].

siRNAs: siRNAs offer a promising approach to diabetes management by targeting specific genes involved in glucagon production or glucose metabolism. Through a process known as RNA interference, siRNAs effectively silence these genes, inhibiting their expression and subsequent protein production. By reducing the levels of glucagon, a hormone that counteracts insulin's glucose-lowering effects, siRNAs can contribute to improved blood sugar control. This therapeutic strategy holds potential for long-term glycemic management [31,32].

Beta glucans: Beta-glucans are dietary fibers that have shown promise in managing blood sugar levels. These complex carbohydrates stimulate the immune system and influence the composition of gut bacteria. A balanced gut microbiome is crucial for overall health, and beta-glucans contribute to this balance by promoting the growth of beneficial bacteria. As a result, the production of short-chain fatty acids (SCFAs) increases. These SCFAs play a pivotal role in enhancing insulin sensitivity, improving the body's ability to absorb glucose from the bloodstream. Additionally, SCFAs strengthen the gut barrier, preventing harmful substances from entering the bloodstream, which indirectly contributes to better blood sugar control [33-35].

Stem cells: Stem cells hold immense promises for diabetes treatment. By undergoing complex developmental processes, they can differentiate into insulin-producing beta cells, effectively replenishing the body's supply. Alternatively, stem cells can stimulate the regeneration of existing beta cells through the release of growth factors and other signaling molecules. These regenerative capabilities offer the potential to restore normal insulin production and alleviate the symptoms of diabetes [36].

A schematic representation of glycemic control mechanism by various biological macromolecules shown in Figure 25.

4. Recent Developments and Future Directions

The field of biological macromolecules in diabetes management is rapidly evolving, with continuous advancements in research and development. Some particularly promising recent developments include:

Dual-agonist molecules: These molecules target multiple receptors related to diabetes, such as GLP-1 and glucagon receptors, simultaneously. This synergistic approach amplifies therapeutic effects and may lead to superior glycemic control with potentially fewer side effects [37,38].

Closed-loop insulin delivery systems: These systems combine microchip technology with continuous glucose monitoring and subcutaneous insulin pumps to create an automated feedback loop for regulating blood sugar levels. This technology potentially minimizes the risk of hypoglycemia and optimizes insulin delivery based on real-time glucose readings [39,40].

Nano-carriers for targeted delivery: Utilizing nano particles for the delivery of biological macromolecules directly to target tissues offers several advantages. Encapsulation protects these molecules from degradation, facilitates specific targeting to relevant cell types, and potentially reduces systemic side effects [41].

Gene editing technologies: CRISPR-Cas9 and other gene editing tools hold immense potential for permanent correction of genetic defects associated with diabetes. Precise manipulation of genes involved in beta cell function or insulin resistance could offer curative solutions in the future [42].

A comprehensive overview of macromolecules, their clinical trial applications, and study outcomes has been presented in tabular format, Table 1. This summary encapsulates key details regarding various macromolecules, including their specific roles in clinical studies, study designs, and significant findings. By providing a structured overview, the table facilitates a clear understanding of the therapeutic potential of these molecules in different disease contexts.

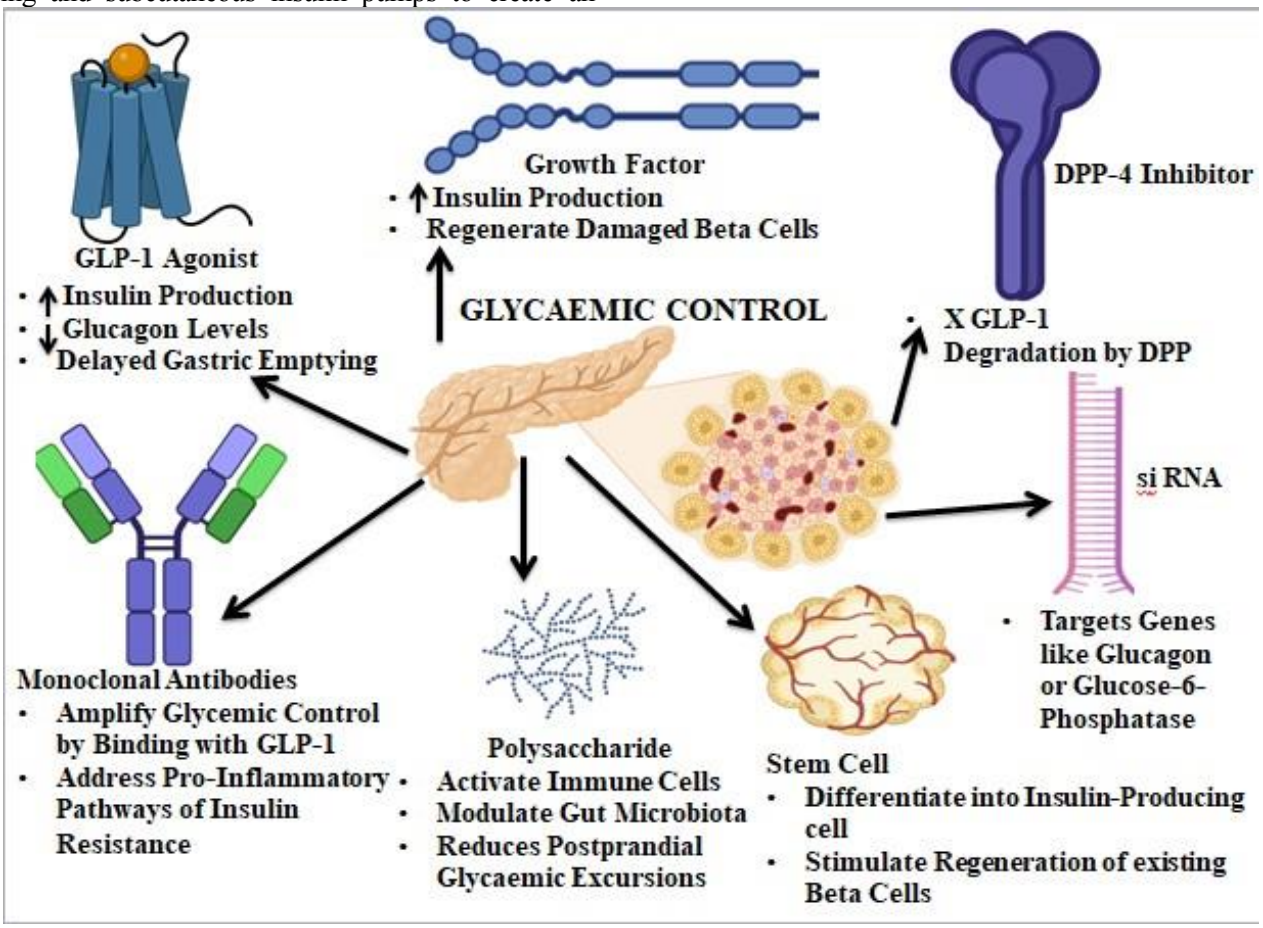

Figure 25. Schematic representation of glycemic control by various macromolecules

Table 1. Detail description of various clinical trial conducted with macromolecules and their study findings.

Sr. No.	Macro-molecule	Study description	Study findings	Reference
1.	**Semaglutide**	Discovery, stages of development, role in pharmacotherapy, clinical research, useful considerations, latest advancements, and effectiveness of semaglutide.	Several clinical trials on adults, the elderly, and obese type 2 diabetes patients, with or without renal/hepatic disease or cardiovascular disease, have conclusively demonstrated the anti-hyperglycemic effect of semaglutide. Semaglutide is generally well tolerated despite its considerable frequency of gastrointestinal adverse effects. Semaglutide improves blood sugar regulation and promotes good patient adherence in monotherapy, with a low risk of hypoglycemia. Several crossover studies have demonstrated that semaglutide does not affect the bioavailability of lisinopril, atorvastatin, furosemide, digoxin, rosuvastatin, warfarin, omeprazole, or oral contraceptives.	**[43]**
2.	**Liraglutide**	Pharmacodynamics and Pharmacokinetics in Type 2 Diabetes Mellitus	Liraglutide, which is mediated by increased insulin and decreased glucagon levels, improved postprandial glycemic management and fasting. Liraglutide is linked to decreased calorie intake and appetite, which leads to weight reduction, as well as positive changes in postprandial lipid profiles. Liraglutide is appropriate for once-daily dosage because of its longer plasma t½ of around 13 hours. Drugs combined administration with liraglutide do not show any serious changes. For individuals with severe or end-stage chronic kidney disease or hepatic impairment, liraglutide is contraindicated or can only be administered with care.	**[44]**
		The effect of liraglutide on patients with or without heart failure with type 2 Diabetes Mellitus	Liraglutide did not increase the chance of heart attack or stroke when compared to a placebo. Also, despite baseline heart failure state, liraglutide reduced rates of MACE (major adverse cardiovascular events), nephropathy, and death compared to placebo. Overall, the analysis of the LEADER data suggests that liraglutide is a good therapy option for type 2 diabetes.	**[45]**
3.	**Exenatide**	The effectiveness of injecting exenatide once every week in children and teenagers with type 2 diabetes.	When compared to a placebo, the once weekly exenatide showed superiority in glycemic control improvement in young people with type 2 diabetes whose condition was not well managed with existing therapies. Significantly, exenatide taken once a week was well accepted and had a safety profile similar to that of adults. The findings underscore the difficulties in treating youth-onset type 2 diabetes and provide support for once-weekly exenatide as a novel therapy option for kids and teenagers.	**[46]**
4.	**Dulaglutide**	The study was conducted to assess the practical efficacy of dulaglutide, particularly in a specific group of type 2 diabetes patients	Dulaglutide's efficacy in lowering body weight and HbA1c (glycated hemoglobin) was remarkably identical to the results of phase III RCTs. Dulaglutide especially contributes to be quite beneficial among women, very old individuals, those with CKD (chronic kidney disease), and people who are not	**[47]**

		that is inadequately represented in RCTs.	obese. Dulaglutide does not interact with other factors, such as concurrent drug use or the presence of cardiovascular or renal disease when it comes to lowering HbA1c. The outstanding cardiovascular protective effects of dulaglutide is highly significant.	
5.	**Sitagliptin**	Confirming the long-term risk-benefit profile of sitagliptin provided to Japanese patients with type 2 diabetes mellitus under real-world conditions was done through post-marketing surveillance (PMS) research.	The long-term and large-scale PMS (post-marketing surveillance) results show that actual areas of treatment and those linked to earlier clinical trials and observational studies have comparable sitagliptin consumption patterns, as well as predicted safety and effectiveness. Sitagliptin shows a small percentage of adverse drug-related events and able to maintain excellent glycemic control while lowering the number of simultaneous drugs. The lack of concerns raised about long-term hazards, such as pancreatitis, cardiovascular events, and reduced renal function, indicates that sitagliptin treatment for an extended period is safe and tolerable for Japanese patients with type 2 diabetes.	**[48]**
6.	**Linagliptin**	The impact of the selective DPP-4 inhibitor linagliptin on renal and cardiovascular outcome s in individuals with type 2 diabetes who are at high risk of renal and cardiovascular (CV) complications.	The main finding of the broad, multicenter, randomized clinical trial, which included patients with type 2 diabetes at high risk of cardiovascular events and high prevalence of kidney disease, was 3-point MACE; linagliptin added to usual care was non-inferior to placebo added to usual care, and no evidence of CV benefit was found. In the same way, linagliptin had no significant impact on the occurrence of the secondary renal composite outcome as compared to a placebo.	**[49]**
7.	**Fibroblast growth factor**	The study investigated the connections between this hepatokine and diseases associated with obesity, as well as the possibility that FGF21 predicts metabolic syndrome in individuals with type 2 diabetes and its interactions with metabolic markers.	When compared to T2DM patients without metabolic syndrome, those with metabolic syndrome exhibit significantly higher FGF21 concentrations along with a higher percentage of women, a higher prevalence of hypertension and elevated blood pressure, elevated body adiposity items, unfavorable lipid, glucose, and kidney functioning, and increased insulin resistance parameters. In the population with type 2 diabetes, FGF21 levels are negatively connected with estimated glomerular filtration rate and positively correlated with body fat mass and serum triglyceride level.	**[50]**
8.	**Hepatocyte growth factor**	Study for the relation between insulin resistance and increased mass of islets / hyperinsulinemia, where hepatocyte growth factor (HGF) plays a crucial role.	A robust and statistically significant link has been seen between HGF and islet hyperplasia/insulin levels across several insulin resistance models, suggesting that this association is constant. There was a definite response for the effect of HGF on increased islet mass, and an increase in HGF levels appeared to occur both before and after the compensatory response linked to insulin resistance.	**[51]**
9.	**Lixisenatide**	This study investigates how Lixisenatide affects people with type 1	In type 1 diabetes patients, lixisenatide did not significantly alter the pre-specified primary endpoint of the proportion of continuous glucose monitoring (CGM) after a 4-week exposure. At the finish line of	**[52]**

		diabetes (T1D) on post-meal glucose excursions and glucagon.	the lixisenatide treatment period, it was seen that much less insulin was being utilized to reach the same time range after meals. Despite the short treatment duration of 4 weeks, there was a significant decrease in the average body weight following lixisenatide therapy.	
10.	**Adalimumab**	The impact of the anti-TNF-α medication adalimumab on the levels of TNF-α and glucose in rats with diabetes caused by streptozotocin (STZ).	In this study, the diabetic group reported more serum interleukin-6 concentrations than the control group. It indicates that some underlying alterations that lead to the development of diabetes may be caused by interleukin-6. The anti-TNF-α drug adalimumab was introduced to lower the blood sugar level in diabetic rats. This suggests that it may have therapeutic value in regulating TNF-α and blood sugar.	**[53]**
11.	**Nucleic Acid**	Effect of Functional Nucleic acids on diabetic Complications therapy	Novel prospects for the detection and treatment of diabetes problems have been made possible by recent developments in functional nucleic acid materials. Functional nucleic acids have autonomous structural roles that allow them to carry out particular biological non-genetic tasks and take the place of conventional proteases and antibodies. Evaluations of functional nucleic acids for diabetic problems mostly focus on tFNA, miRNA, and siRNA. Additionally, drug-loaded tFNA may contribute to a variety of diabetes problems.	**[54]**
12.	**Polysaccharides**	Study about the anti-diabetic properties of polysaccharide and regulate the gut microbiota.	Due to its significant connection to diabetes mellitus, the gut microbiota is increasingly being targeted for DM therapy. The gut microbiota ferments polysaccharides to generate SCFAs and other metabolites that might help to overcome diabetic conditions. More research is still needed to determine the exact link between polysaccharides and the gut microbiota.	**[55]**
13.	**Stem Cell**	Study about the effectiveness of using stem cells to treat diabetes mellitus shows promise for future diabetes therapies.	Transplanting bone marrow hemopoietic stem cells (BM-HSCs) for type 1 diabetes and bone marrow mononuclear cells (BM-MNCs) with mesenchymal stromal cells (MSCs) for type 2 diabetes established the best therapeutic result. On the other hand, stem cell transplantation is not a suitable option for diabetic ketoacidosis (DKA) patients.	**[56]**

5. Nanoparticles for Diabetes Management: Natural, Synthetic, and Inorganic Approaches

Polymeric nanoparticles (PNPs), both natural and synthetic, along with inorganic nanoparticles, have appeared as advanced approach for diabetes management, contributing improved drug delivery, enhanced bioavailability, and targeted therapeutic action. Natural PNPs, such as those derived from chitosan, dextran, alginate, and albumin, are biocompatible, biodegradable, and mucoadhesive, establishing them perfect for oral insulin delivery and phytocompound administration. For example, chitosan-based nanoparticles defend insulin from gastrointestinal (GI) degradation, attaining up to 17.19% bioavailability in diabetic rats by enhancing paracellular and transcellular transport [57]. Dextran-based nanoparticles, particularly acetalated-dextran, provide glucose-responsive insulin release, maintaining normoglycemia for 16 hours in diabetic mice [58].

Synthetic PNPs, with poly (lactic-co-glycolic acid) (PLGA), poly (lactic acid) (PLA) and hydroxypropyl methylcellulose phthalate (HPMCP), offer tunable properties for accurate drug release. PLGA nanoparticles encapsulating curcumin or insulin demonstrate pulsatile release under high-glucose circumstances, improving glycemic control [59]. HPMCP nanoparticles defend insulin in acidic gastric environments, releasing it in the neutral intestine, with 8.6% bioavailability in preclinical models [60].

Inorganic nanoparticles, such as gold, silver and silica nanoparticles, augment diabetes management through

exclusive mechanisms. Gold nanoparticles conjugated with insulin or GLP-1 agonists improve stability and targeted delivery to pancreatic beta cells, forcing their high surface area and plasmonic properties [61]. Silver nanoparticles, frequently combined with chitosan, show anti-diabetic and wound-healing properties by reducing oxidative stress and microbial infections in diabetic models [62]. Silica nanoparticles, with their porous structure, allow controlled release of metformin or insulin, improving cellular uptake through receptor-mediated endocytosis [63].

The mechanisms of action for these nanoparticles include mucoadhesion, tight junction modulation and stimuli-responsive release (pH or glucose-triggered), which prevent drugs from enzymatic degradation and increase lymphatic acceptance via Peyer's patches [64].

Safety and toxicity remain significant issues. Natural PNPs are usually non-toxic due to their biodegradability, but synthetic PNPs, like PLGA, may produce acidic byproducts, potentially cause inflammation if not appropriately clear [65]. Inorganic nanoparticles, particularly silver, pose risks of cytotoxicity and organ accumulation (e.g., liver and kidneys) at high doses, requiring rigorous dose optimization and long-term toxicity studies [66]. Surface adjustments, such as PEGylation, mitigate toxicity by improving biocompatibility and reducing immune responses [67].

Clinical studies have mainly aimed on polymeric nanoparticles, with limited data on inorganic nanoparticles for diabetes. A phase II trial of PLGA-encapsulated exenatide demonstrated improved glycemic control in type 2 diabetes patients, reducing HbA1c by 1.2% over 12 weeks with negligible adverse effects [68]. Another study on chitosan-insulin nanoparticles showed a 10% bioavailability increase in type 1 diabetes patients, highlighting their potential for oral delivery [69]. Inorganic nanoparticle human studies are less progressive, but a phase I study of gold nanoparticle-conjugated insulin reported enhanced stability and a 15% reduction in insulin dosage necessities in type 1 diabetes patients [70]. Additionally, a clinical trial of silica nanoparticles loaded with metformin exhibited sustained release and a 0.9% HbA1c reduction in type 2 diabetes patients through a period of 8 weeks [71]. Despite these improvements, challenges like scalability, long-term safety and regulatory approval still present, demanding further clinical validation to ensure safe transformation into diabetes management [72].

6. Challenges and Limitations

While the potential of biological macromolecules in diabetes management is vast, certain challenges and limitations need to be addressed.

Cost and Accessibility

The development and production of macromolecules often involve complex and expensive processes. Consequently, the cost of these therapies can be prohibitively high for many patients, leading to significant healthcare disparities. To ensure equitable access to these innovative treatments, strategies to reduce production costs and increase affordability are essential.

Long-Term Safety and Efficacy

While short-term clinical trials have demonstrated the efficacy of many macromolecules in diabetes management, long-term safety and efficacy data are still emerging. It is crucial to conduct extensive follow-up studies to assess the potential for long-term side effects, including immunogenicity and the development of resistance [73].

Personalized Medicine Considerations

To maximize the benefits of macromolecule-based therapies, a deeper understanding of individual patient variability is necessary. Identifying genetic, metabolic, and clinical factors that influence treatment response will enable the development of personalized treatment plans. This precision medicine approach has the potential to improve therapeutic outcomes and reduce adverse events.

Addressing these challenges requires ongoing research, collaboration between academia, industry, and healthcare providers, and policy initiatives to support the development and accessibility of macromolecule-based diabetes therapies [74].

7. Conclusion

The potential of biological macromolecules in the management of diabetes care is truly transformative and undeniable. By addressing the multifaceted nature of this complex disease through precise mechanisms of action, these molecules offer hope for improved glycemic control, reduced complications, and enhanced quality of life for patients with diabetes. Continuous research and development efforts, alongside rigorous clinical trials, are essential to translate these advancements into clinically effective therapies that can significantly impact global diabetes management. By addressing the current challenges in diabetes treatment and building upon the promising advancements in biological macromolecules, researchers can work towards a future where diabetes is effectively controlled, reducing its impact on patients' lives and ultimately aiming for a world free from the disease.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used gemini.google to reduce grammatical errors. After using this tool/service, the author(s) reviewed and edited the content as needed and took full responsibility for the content of the publication.

Ethics Approval and Consent to Participate

Since this manuscript is a review article, formal ethical approval and consent to participate are not applicable.

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Since this is a review article, no primary datasets were generated or analyzed. All data supporting this review are available in the referenced literature.

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