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Exploring Synthetic Peptides as Novel Agents for Antidiabetic Activity and Neuropathy Alleviation

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Abstract
The chronic metabolic disorder known as diabetes mellitus is frequently accompanied by a number of complications, one of which is diabetic neuropathy, which has a significant impact on the quality of life those who suffer from the condition. Existing diabetes treatment methods have a number of drawbacks, including suboptimal control of blood glucose levels and unfavorable side effects. The potential of synthetic peptides as novel therapeutic agents for the management of diabetes and the alleviation of neuropathy is investigated in this review as well. The potential of synthetic peptides as insulin mimetics and sensitizers has been demonstrated. These peptides are designed to interact with insulin signaling pathways and are intended to enhance glucose uptake. As a result of their neuroprotective effects, it is possible that they could reduce inflammation, encourage nerve regeneration, and alleviate the pain that is associated with neuropathy. It is essential for the therapeutic efficacy of these peptides that they have a structural design that is optimized, with a particular emphasis on the amino acid composition, stability, and bioavailability. Recent preclinical studies and clinical trials that are still ongoing provide interesting and useful information regarding their efficacy and safety. The possibility that synthetic peptides have the ability to transform diabetes care and improve patient outcomes by highlighting the multifaceted role that synthetic peptides play in the regulation of metabolism and the relief of neuropathy. When it comes to clinical practice, additional research is necessary in order to fully realize the benefits of synthetic peptide therapies.
Keywords: *diabetes, neuropathy, synthetic peptides, insulin mimetics, neuroprotection, metabolic regulation, glucose uptake.*

1. Introduction

Insulin resistance, inadequate production of insulin, or a combination of the two, causes hyperglycemia, a condition marked by elevated blood sugar levels. Diabetes is a chronic metabolic disorder. Chronic high blood sugar levels have the potential to cause a number of problems that can impact different organ systems over time. Diabetic neuropathy is a condition that mainly affects the peripheral nervous system and is one of the most common and crippling side effects. The quality of life that a patient experience can be greatly affected by neuropathy, which can cause symptoms like pain, tingling, and loss of sensation, frequently beginning in the hands and feet. Diabetic retinopathy, kidney damage, wound healing deficiencies that can result in amputations and infections, and nephropathy are additional complications. Managing blood glucose levels is the mainstay of diabetes treatment strategies, with the goal of delaying or preventing the development of complications. In addition to oral drugs (such as metformin and sulfonylureas) and insulin therapy, these treatments involve lifestyle changes like diet and exercise. But even with these treatments, a lot of patients still have trouble keeping their blood sugar under control, which raises the possibility of long-term problems. Addressing symptoms and attempting to halt progression are the specific goals of managing diabetic neuropathy. Neuropathic pain

management often involves the use of painkillers, such as topical treatments, anticonvulsants, antidepressants, and nonsteroidal anti-inflammatory drugs (NSAIDs). These medications, however, frequently only offer a partial cure and may have unfavorable side effects like weariness, dependency, or dizziness. And once nerve damage has occurred, there is currently no known cure that can completely undo the damage. Because of this, there is an increasing need for cutting-edge therapeutic strategies that improve outcomes for diabetic patients by addressing the underlying causes of complications like neuropathy in addition to controlling blood sugar levels [3,4].

1.1 Synthetic Peptides for Diabetes and Neuropathy Relief

Peptides are synthetic amino acid chains that mimic body proteins. Chemical processes control amino acid arrangement to create highly specific peptides with specific biological functions. Small size and ability to be tailored for stability and targeted interactions make them useful in medical research. The ability of synthetic peptides to engage with specific cellular pathways has made them useful in cancer treatment, hormone replacement, vaccine development, and immunotherapy. To overcome the limitations of current diabetes and neuropathy treatments, synthetic peptides are appealing. Alternative insulin therapy for diabetes can be provided by synthetic peptides, which mimic insulin or increase insulin sensitivity. They can better control blood sugar by interacting with glucose metabolism components. Neuroprotection, inflammation reduction, and nerve tissue regeneration are possible with synthetic peptides for diabetic neuropathy. Neuropathy treatments currently focus on symptom relief, which is ineffective and has side effects. Alternatively, synthetic peptides may directly target the molecular mechanisms of neuropathy, relieving pain and addressing nerve damage. Synthetic peptides may improve diabetes and neuropathy management due to their precise mode of action. Synthetic peptides, chains of amino acids that mimic body proteins, contain many therapeutic uses. Chemical methods can precisely control amino acid sequences to create peptides with specific biological functions. Synthetic peptides are useful in modern medicine due to their flexibility. Researchers can design peptides that interact with specific receptors or enzymes to treat various conditions by altering their structure. These peptides are used in oncology, immunotherapy, endocrinology, and infectious disease research. Engineered stability and bioavailability boost their drug efficacy. Unique properties justify exploring synthetic peptides for diabetes and neuropathy relief. Enhanced insulin sensitivity or glucose metabolism can be achieved by synthetic peptides in diabetes management. Unlike current treatments that require frequent administration and have side effects, synthetic peptides may better control blood sugar levels. By reducing inflammation and promoting nerve regeneration, these peptides may protect neuropathy. This makes them useful in treating diabetic neuropathy, which causes nerve damage and chronic pain. A promising new approach to blood sugar management and neuropathy prevention is synthetic peptides' ability to target specific molecular pathways [1,2].

2. Pathophysiology of Diabetes and Neuropathy

2.1 Diabetes progression and metabolic dysfunction

The development of diabetes affects the body's capacity to properly regulate blood glucose through intricate processes that result in metabolic dysfunction. An autoimmune reaction that targets and kills the pancreatic beta cells responsible for producing insulin is the main cause of type 1 diabetes. Insulin, which is necessary to transfer glucose from the bloodstream into cells, is completely destroyed as a result of this destruction. When glucose levels are not properly controlled, they rise sharply, leading to a variety of symptoms as well as long-term issues. On the other hand, insulin resistance a condition in which the bodys cells do not react to insulin as they should is how Type 2 diabetes arises. Usually, obesity, sedentary lifestyles, and genetic predispositions combine to cause this resistance to develop. For a while, the pancreas initially produces more insulin to offset this resistance, which keeps blood

sugar levels normal. But over time, elevated glucose levels may result from the pancreas' inability to maintain sufficient insulin production in response to an increase in insulin demand. Beyond just the metabolism of glucose, diabetes-related metabolic dysfunction also interferes with other pathways. An unhealthy lipid metabolism can lead to elevated triglyceride and cholesterol levels, which raise the risk of cardiovascular disease. Moreover, protein metabolism is impaired, which results in changes to muscle mass and total energy expenditure. The body experiences a series of detrimental consequences when blood sugar levels are consistently elevated. Oxidative stress is associated with persistent hyperglycemia and arises from an imbalance between antioxidants and free radicals. This disease ultimately results in complications like diabetic neuropathy, retinopathy, and nephropathy by exacerbating blood vessels and nerves and causing inflammation. Developing targeted therapeutic strategies requires an understanding of the underlying mechanisms underlying the progression of diabetes and metabolic dysfunction. For those with diabetes, good management can reduce their risk of complications, enhance their quality of life, and improve their overall health results [5,6].

2.2 Role of oxidative stress and inflammation

Synthetic peptides are extremely important in the regulation of metabolism because they mimic the actions of insulin and significantly increase the amount of glucose that is taken up by peripheral tissues. Insulin signaling pathways are influenced by their interactions, which results in increased insulin sensitivity and the promotion of metabolic homeostasis. When it comes to the management of diabetes and the optimization of glucose metabolism, their potential as targeted therapeutic agents offers potential avenues that hold great promise. Significance of Oxidative stress and inflammation are as shown in the figure 1.

- *Oxidative Stress*: Reactive oxygen species (ROS) production and the body's capacity to remove these damaging substances via antioxidants are out of balance, which is known as oxidative stress. Hyperglycemia causes more reactive oxygen species (ROS) to be produced, which oxidizes proteins, lipids, and DNA in diabetics. Retinopathy, neuropathy, and cardiovascular disease are among the consequences that arise from this cellular damage, which also affects blood vessels, nerves, and organs. In addition to directly harming cells, the chronic oxidative stress associated with diabetes also starts other harmful pathways, making management of the condition more difficult.

- *Inflammation*: Diabetes patients experience inflammation as a result of chronic oxidative stress. TNF-α, IL-6, and IL-1β are among the pro-inflammatory cytokines that are produced and released when ROS levels are elevated. These pathways are activated by inflammatory factors. Prolonged inflammation impedes normal physiological functions and adds to tissue deterioration. As glial cells become activated in the nervous system, inflammatory mediators are secreted, exacerbating nerve damage and resulting in neuroinflammation. Diabetic neuropathy symptoms are exacerbated by this inflammatory milieu, which also makes nerve regeneration and repair difficult.

- *Nerve Damage*: One important side effect of diabetes is nerve damage, which happens to be especially noticeable in diabetic neuropathy cases. Via glycation, which occurs when too much glucose binds to proteins and lipids and changes their normal structure and function, high blood sugar levels can directly harm nerve fibers. An inability to sense pain, tingling, or loss of sensation can result from this glycation process disruption of nerve signaling. Because the blood-nerve barrier is essential for preserving a stable environment for nerve function, the

inflammatory response linked to diabetes plays a further role in nerve damage. Due to this breakdown, the nerves are less able to receive vital nutrients and are more vulnerable to damage.

- *Vicious Cycle*: Complications associated with diabetes are made worse by the interaction of oxidative stress, inflammation, and nerve damage. While inflammation can exacerbate oxidative damage and result in more severe tissue injury, oxidative stress can also cause inflammation. Ultimately, this feedback loop causes a reduction in general health and raises the possibility of consequences like kidney damage, cardiovascular disease, and diabetic neuropathy. Effective diabetes management and better patient outcomes depend on breaking this cycle.

- *Therapeutic Implications*: One potentially effective approach to reducing the complications linked to diabetes is to focus on inflammation and oxidative stress. Metabolic health can be improved and oxidative damage can be decreased by interventions that strengthen the body's antioxidant defenses, such as dietary modifications or prescription drugs. Anti-inflammatory treatments may lessen the ongoing inflammation linked to diabetes, which may delay the development of nerve damage and other consequences. Novel treatment strategies can lessen the burden of diabetes's long-term consequences and improve the quality of life for those who have the disease by targeting these interrelated processes.

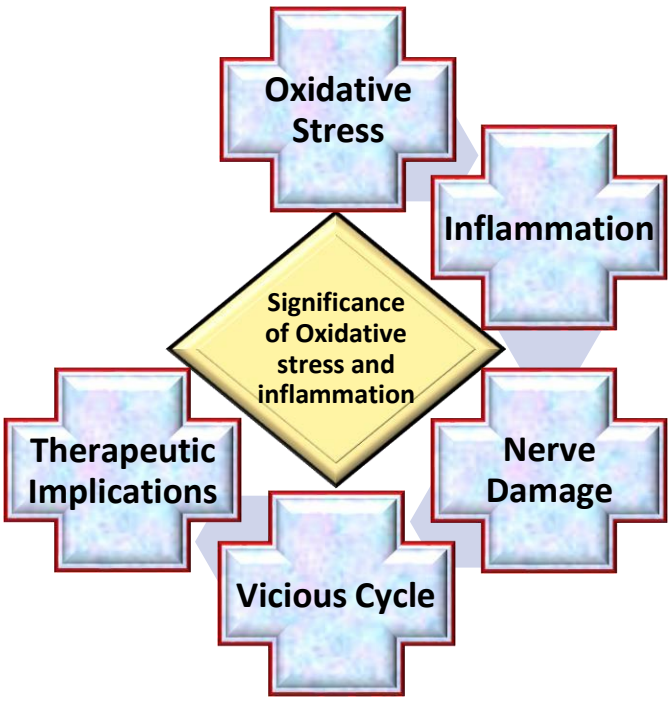

Figure 1: Significance of Oxidative stress and inflammation

3. Role of Synthetic Peptides in Metabolic Regulation

3.1 Peptide-insulin pathway interaction

The regulation of insulin signaling pathways, glucose uptake, and metabolic function by peptides offers promising diabetes treatments. The interaction of synthetic peptides with target cell insulin receptors is

important. Peptides that bind to the insulin receptor activate intracellular signaling cascades, including the PI3K pathway. After activation, glucose transporter proteins like GLUT4 are recruited to the cell membrane, allowing glucose to enter muscle and adipose tissues. Synthetic peptides can also lower blood sugar by activating insulin receptors, making them a viable hyperglycemia treatment. Besides mimicking insulin, synthetic peptides can directly affect glucose transporters, improving functions. Specific peptides can target GLUT4 or GLUT1 transporters to improve glucose uptake into cells. Direct modulation is beneficial in insulin resistance, where insulin signaling may be impaired. Synthetic peptides improving glucose uptake improves glycemic regulation and cellular energy utilization, which is essential for metabolic health. Synthetic peptides interfere with gluconeogenesis, a liver metabolic process that synthesizes glucose from non-carbohydrate sources. These peptides lower gluconeogenic enzyme expression, reducing hepatic glucose output and stabilizing blood sugar, especially during fasting or physiological demand. Diabetes sufferers need this mechanism to avoid hyperglycemia. Peptides can also enhance fat metabolism by promoting fat use for energy and reducing fat accumulation. Some synthetic peptides induce lipolysis, which converts stored lipids into energy-producing fatty acids. This modulation of lipid metabolism helps manage weight and improves insulin sensitivity, as excess body fat increases insulin resistance. Some synthetic peptides mimic gut incretins, which regulate food intake. Incretin-like peptides increase insulin secretion and inhibit glucagon release, regulating post-meal glucose. They also promote fullness, which can reduce food intake and improve weight management, supporting metabolic health. Anti-inflammatory properties may boost glucose metabolism in synthetic peptides. These peptides reduce inflammatory markers to restore insulin signaling and glucose homeostasis. The complex role of synthetic peptides in regulating glucose levels, lipid metabolism, and inflammation makes them promising candidates for innovative therapies to improve glycemic control and reduce diabetes and metabolic disorder complications [7,8,9].

4. Synthetic Peptides in Neuropathy Relief

4.1 Neuroprotective effects of synthetic peptides

Synthetic peptides have a variety of neuroprotective effects, which are as shown in the figure 2 that can improve outcomes and protect neurons in conditions like diabetic neuropathy and other neurodegenerative disorders. These effects can range from lowering oxidative stress and inflammation to enhancing neurotrophic signaling and promoting nerve regeneration.

- *Reduction of Oxidative* Stress: Reactive oxygen species (ROS) are the cause of neuronal injury and degeneration; synthetic peptides act as potent antioxidants by scavenging ROS. Raised ROS concentrations have the potential to cause oxidative damage to neuronal cells, which can impact DNA, proteins, and lipids. Synthetic peptides assist in reducing this oxidative damage by increasing the activity of endogenous antioxidant enzymes, saving the integrity and function of the neurons. By halting the advancement of neurodegenerative illnesses and reducing diabetic neuropathy symptoms, this defense system promotes better neuronal health and function.

- *Modulation of Inflammatory Responses*: An important factor in neurodegeneration and nerve damage is chronic inflammation of the nervous system. Because pro-inflammatory cytokines are signaling molecules that prolong inflammation, synthetic peptides can be extremely important in modulating inflammatory responses. The activation of glial cells, which can worsen neuroinflammation, is also inhibited by these peptides. Synthetic peptides protect neurons from inflammatory damage and also improve overall recovery by promoting healing

processes in affected tissues and fostering a more favorable microenvironment for nerve repair and regeneration.

- *Enhancement of Neurotrophic Signaling*: Because neurotrophic factors are essential for the development, differentiation, and survival of neurons, some synthetic peptides have the ability to mimic the effects of these factors, including brain-derived neurotrophic factor (BDNF). Neurotrophic factor expression is enhanced by these peptides because they activate intracellular signaling pathways that support neurogenesis and cell survival. Synthetic peptides maintain the health of neurons by enhancing neurotrophic signaling, which in turn promotes resilience against neurodegenerative processes and increases the likelihood of recovery after nerve damage [10].

- *Promotion of Nerve* Regenerati: Artificial peptides have the ability to trigger different cellular mechanisms that help injured nerves heal and regenerate. Peripheral nerve regeneration depends on the migration of Schwann cells, which they stimulate. Extracellular matrix components that give regenerating axons structural support can be synthesized more effectively by synthetic peptides. When these two actions are combined, nerve injury and conditions like diabetic neuropathy can be healed more quickly and with better functional outcomes.

- *Regulation of Calcium Homeostasis*: One of the main causes of neuronal damage and a contributing factor to a number of neurodegenerative illnesses is calcium dysregulation. Calcium influx and efflux are modulated by synthetic peptides, which contribute to the preservation of calcium homeostasis in neurons. Excitotoxicity is a process where an excessive calcium influx results in cell death; this regulation is crucial to preventing it. Synthetic peptides play a vital role in maintaining the overall health of the nervous system by promoting cellular survival and protecting against neuronal damage by maintaining balanced calcium levels.

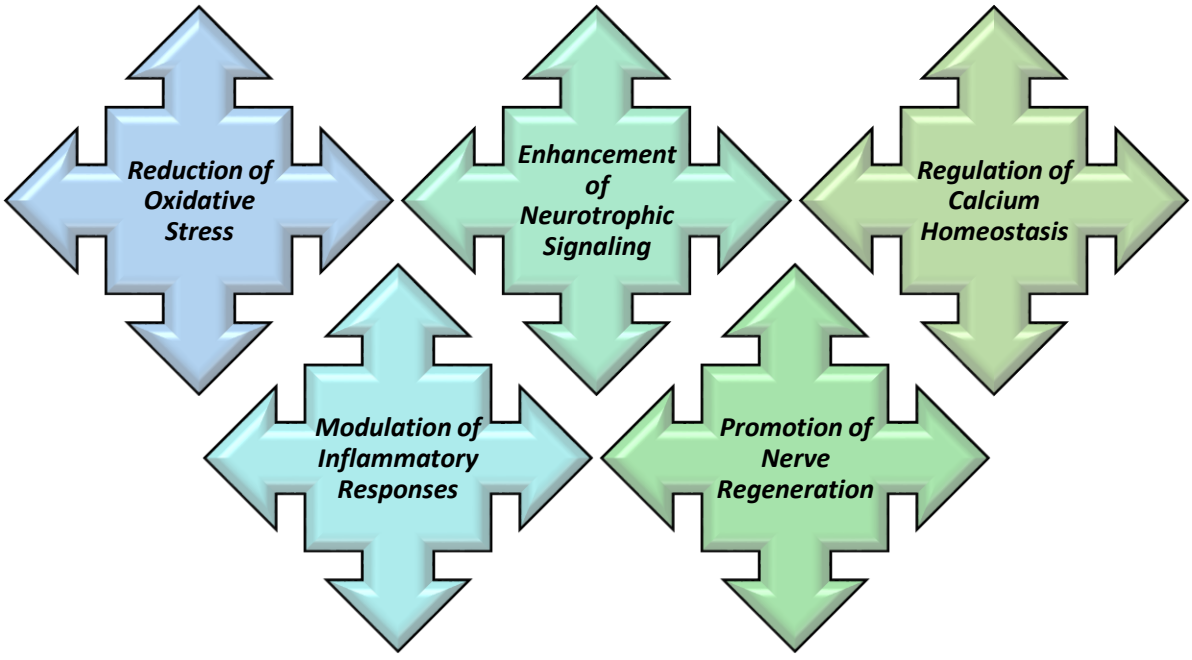

Figure 2: Neuroprotective Properties of Synthetic Peptides

5. Peptide Design and Optimization

Creating synthetic peptides with specific antidiabetic activity in mind is crucial to creating therapeutic agents that work. In order to achieve the best possible interactions with insulin receptors and other important targets involved in glucose metabolism, this design meticulously selects amino acid sequences. Stability and solubility must be taken into account when selecting the amino acid composition in order to maximize receptor binding affinity. Peptides balance stability and bioactivity with lengths typically between 10 and 20 amino acids. Changes to the peptide's structure, such as cyclization or the addition of non-canonical amino acids, can strengthen its resistance to enzymatic breakdown and increase its binding efficiency. Furthermore, peptides can be engineered to take on advantageous three-dimensional conformations, such as beta-sheets or alpha-helices, which will increase their biological activity. Improving synthetic peptides' bioavailability, stability, and specificity is essential to their effective use as medicinal agents. Changing the peptide structure is one way to make it more resistant to enzymatic degradation. Cyclization or the addition of D-amino acids, which are resistant to proteolytic enzymes, can accomplish this. Peptides can be formulated with delivery systems like liposomes or nanoparticles to increase their bioavailability and ensure that they reach the target tissues efficiently. By designing peptides with targeting motifs that promote receptor-mediated uptake into targeted cells and lessen off-target effects, specificity can be increased. SAR studies and high-throughput screening are two examples of advanced techniques that are frequently used to find the best peptide candidates with improved pharmacokinetic properties. To create medications that promote nerve regeneration and alleviate neuropathic pain, peptide engineering is essential. Peptides can be engineered to display neuroprotective properties that lower oxidative stress and inflammation in the nervous system by carefully planning and optimizing them. Synthetic peptides that contain sequences that resemble neurotrophic factors can promote neuronal survival and nerve growth. Peptide engineering additionally permits the modification of binding affinities to particular receptors involved in pain signaling pathways, allowing for the targeted alleviation of neuropathic pain. Advances in computational modeling and peptide synthesis methodologies facilitate the production of peptides with specific characteristics, thereby opening the door to neuropathy and associated ailments being effectively treated. All things considered, peptide engineering is a potent tool that is helping to advance treatment approaches for neuropathy and diabetes and is opening up exciting new clinical application opportunities [11,12,13].

6. Preclinical and Clinical Studies

In models of diabetes and neuropathy, preclinical research is essential to assessing the therapeutic potential of synthetic peptides. Synthetic peptides have been shown in multiple studies to improve overall metabolic control, lower blood glucose levels, and significantly increase insulin sensitivity in diabetic animal models. To promote glucose uptake in peripheral tissues, for instance, some peptides have demonstrated the capacity to mimic the actions of insulin. Furthermore, synthetic peptides have shown neuroprotective effects in neuropathy models, lowering oxidative stress and inflammation, easing pain, and encouraging nerve regeneration. With their potential to address the complexities of both diabetes and neuropathic conditions, these preclinical findings offer a solid foundation for the advancement of peptide-based therapies into clinical trials. The effectiveness and safety of using synthetic peptides to treat diabetes and neuropathy are currently being studied in a number of clinical trials as research advances. In order to ascertain the therapeutic benefits of different peptide formulations, dosage schedules, and administration methods, these trials evaluate them. Promising results are being observed in some ongoing trials, where participants are showing reduced neuropathic symptoms and improved glycemic control. As an example, peptide therapies have been linked to

decreased HbA1c levels and increased insulin sensitivity in individuals with diabetes. To draw firm conclusions about the usefulness and efficacy of these treatments in a range of patient populations, however, extensive data from larger, multi-center trials are required. When developing peptide-based treatments, it is critical to assess both safety and efficacy. Even though a lot of synthetic peptides have demonstrated therapeutic promise, it's crucial to comprehend their safety profiles to guarantee patient welfare. The majority of research suggests that, in comparison to traditional treatments, synthetic peptides are typically well-tolerated and have a lower risk of serious side effects. On the other hand, gastrointestinal issues, injection site-specific reactions, or mild allergic reactions are possible adverse effects. To evaluate the long-term safety and tolerability of these agents, it is imperative to continuously monitor adverse events that occur during clinical trials. Clinical guidelines and the best possible use of synthetic peptides in the treatment of diabetes and neuropathy will ultimately come from a complete understanding of the safety, effectiveness, and possible adverse effects. This will open the door to new therapeutic options [14,15].

Conclusion

A potential treatment option for diabetes and its sequelae, including neuropathy, is synthetic peptides. Novel therapeutic approaches are required due to the complex mechanisms that underlie the progression of diabetes and the incapacitating effects of neuropathy. Even though they are somewhat successful, the side effects and difficulty in attaining ideal glycemic control frequently pose limitations to current treatment modalities. Because synthetic peptides function as insulin sensitizers or imimetics, they present a novel therapeutic option that may improve metabolic regulation without the side effects of conventional treatments. Preclinical and clinical research provide evidence of the neuroprotective properties of synthetic peptides, indicating their capacity to reduce inflammation, stimulate nerve regeneration, and modulate pain. These peptides structural design and optimization are essential because particular amino acid compositions and modifications can greatly improve their stability, bioavailability, and targeting potential. The safety and effectiveness of peptide-based therapies is opening the door to more effective treatments by shedding light on their therapeutic potential. Future prospects for treating diabetes and its complications are promising thanks to the introduction of synthetic peptides into clinical practice. Peptide engineering and thorough clinical assessments will clarify their function in enhancing patient outcomes. The complexities of diabetes and neuropathy, the development of synthetic peptides is a major step forward and gives hope for more individualized and effective therapeutic interventions.

References

1. Katsarou, A.; Gudbjörnsdottir, S.; Rawshani, A.; Dabelea, D.; Bonifacio, E.; Anderson, B.J.; Jacobsen, L.M.; Schatz, D.A.; Lernmark, A. Type 1 Diabetes Mellitus. *Nat. Rev. Dis. Primer* **2017**, *3*.
2. DeFronzo, R.A.; Ferrannini, E.; Groop, L.; Henry, R.R.; Herman, W.H.; Holst, J.J.; Hu, F.B.; Kahn, C.R.; Raz, I.; Shulman, G.I.; et al. Type 2 Diabetes Mellitus. *Nat. Rev. Dis. Primer* **2015**, *1*, 1–22.
3. Fletcher, B.; Gulanick, M.; Lamendola, C. Risk Factors for Type 2 Diabetes Mellitus. *J. Cardiovasc. Nurs.* **2002**, *16*, 17–23.
4. Taylor, S.I.; Yazdi, Z.S.; Beitelshees, A.L. Pharmacological Treatment of Hyperglycemia in Type 2 Diabetes. *J. Clin. Investig.* **2021**, *131*.
5. Quinn, L. Mechanisms in the Development of Type 2 Diabetes Mellitus. *J. Cardiovasc. Nurs.* **2002**, *16*, 1–16.
6. Geraldes, P.; King, G.L. Activation of Protein Kinase C Isoforms and Its Impact on Diabetic Complications. *Circ. Res.* **2010**, *106*, 1319–1331.

7. Yamagishi, S.; Imaizumi, T. Diabetic Vascular Complications: Pathophysiology, Biochemical Basis and Potential Therapeutic Strategy. *Curr. Pharm. Des.* **2005**, *11*, 2279–2299.
8. American-Diabetes-Association. Standards of Medical Care in Diabetes. *Diabetes Care* **2020**, *43*, S1–S207.
9. Nishikawa, T.; Edelstein, D.; Du, X.L.; Yamagishi, S.I.; Matsumura, T.; Kaneda, Y.; Yorek, M.A.; Beebe, D.; Oates, P.J.; Hammes, H.P.; et al. Normalizing Mitochondrial Superoxide Production Blocks Three Pathways of Hyperglycaemic Damage. *Nature* **2000**, *404*, 787–790.
10. Umpierrez, G.; Korytkowski, M. Diabetic Emergencies-Ketoacidosis, Hyperglycaemic Hyperosmolar State and Hypoglycaemia. *Nat. Rev. Endocrinol.* **2016**, *12*, 222–232.
11. Borska, S.; Sopel, M.; Chmielewska, M.; Zabel, M.; Dziegiel, P. Quercetin as a Potential Modulator of P-Glycoprotein Expression and Function in Cells of Human Pancreatic Carcinoma Line Resistant to Daunorubicin. *Molecules* **2010**, *15*, 857–870.
12. Rom, S.; Heldt, N.A.; Gajghate, S.; Seliga, A.; Reichenbach, N.L.; Persidsky, Y. Hyperglycemia and Advanced Glycation End Products Disrupt BBB and Promote Occludin and Claudin-5 Protein Secretion on Extracellular Microvesicles. *Sci. Rep.* **2020**, *10*, 7274.
13. Choudhury, H.; Pandey, M.; Hua, C.K.; Mun, C.S.; Jing, J.K.; Kong, L.; Ern, L.Y.; Ashraf, N.A.; Kit, S.W.; Yee, T.S.; et al. An Update on Natural Compounds in the Remedy of Diabetes Mellitus: A Systematic Review. *J. Tradit. Complement. Med.* **2017**, *8*, 361–376.
14. Bhaskar, V.; Goldfine, I.D.; Bedinger, D.H.; Lau, A.; Kuan, H.F.; Gross, L.M.; Handa, M.; Maddux, B.A.; Watson, S.R.; Zhu, S.; et al. A Fully Human, Allosteric Monoclonal Antibody That Activates the Insulin Receptor and Improves Glycemic Control. *Diabetes* **2012**, *61*, 1263–1271.
15. Xiao, C.; Kim, H.-S.; Lahusen, T.; Wang, R.-H.; Xu, X.; Gavrilova, O.; Jou, W.; Gius, D.; Deng, C.-X. SIRT6 Deficiency Results in Severe Hypoglycemia by Enhancing Both Basal and Insulin-Stimulated Glucose Uptake in Mice. *J. Biol. Chem.* **2010**, *285*, 36776–36784.