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HYPOGLYCEMIC ACTIVITY OF COMPOUNDS CONTAINED IN OLIGOPEPTIDES DERIVED FROM BOMBYX MORI (LITERATURE REVIEW)

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Abstract

Diabetes mellitus is one of the most widespread chronic endocrine diseases and represents a serious medical, social, and economic problem worldwide. In recent years, particular attention has been paid to bioactive compounds of natural origin that exhibit hypoglycemic, antioxidant, and metabolic effects. Among such compounds are oligopeptides derived from *Bombyx mori* (silkworm). This literature review is devoted to the analysis of current data on the hypoglycemic activity of compounds included in oligopeptides from *Bombyx mori*, their possible mechanisms of action, pharmacological potential, and prospects for application in diabetes mellitus. It has been shown that these compounds are capable of improving glucose tolerance, increasing insulin sensitivity, reducing oxidative stress, and inhibiting key enzymes such as α-glucosidase, α-amylase, and DPP-4. Despite significant preclinical progress, further toxicological, pharmacokinetic, and clinical studies are required for the introduction of these biomolecules into clinical practice.

Keywords: diabetes mellitus, *Bombyx mori*, oligopeptides, hypoglycemic activity, antioxidant effect, insulin resistance, α-glucosidase, DPP-4, AMPK, GLUT4

Introduction

Diabetes mellitus (DM) is a chronic endocrine disease characterized by impaired insulin secretion, reduced tissue sensitivity to insulin, or a combination of both mechanisms [1–3]. As a result, disturbances in carbohydrate, lipid, and protein metabolism develop, leading to severe systemic complications.

According to data presented in recent literature, by 2024 approximately 589 million adults aged 20–79 years worldwide are affected by diabetes, and by 2050 this number is expected to reach 853 million. In Uzbekistan, a steady increase in the number of patients has also been observed, with more than 1 million registered cases of diabetes [4–6].

Despite the availability of a wide range of synthetic antidiabetic drugs, their long-term use is associated with several limitations, including the risk of hypoglycemia, adverse effects, reduced

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efficacy, and high cost of certain drug classes. Therefore, there is growing interest in the search for new hypoglycemic agents of natural origin with high safety and multimodal mechanisms of action. One of the promising directions is the study of bioactive oligopeptides derived from proteins of the silkworm *Bombyx mori* [7].

Diabetes Mellitus as a Global Medical and Social Problem

Diabetes mellitus is classified into two main types. Type 1 DM is primarily associated with autoimmune destruction of pancreatic β-cells and absolute insulin deficiency. In contrast, type 2 DM is characterized by a combination of relative insulin deficiency and insulin resistance.

A key role in the pathogenesis of type 2 diabetes is played by disturbances in IRS-1 and PI3K/Akt signaling pathways, decreased expression of GLUT4, chronic inflammation, oxidative stress, mitochondrial dysfunction, and lipotoxicity [8–9].

Modern pharmacological approaches to diabetes treatment include the use of biguanides, sulfonylurea derivatives, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists. However, none of these drug groups is completely free from limitations. For example, sulfonylureas may cause hypoglycemia, SGLT2 inhibitors increase the risk of urinary tract infections, and GLP-1 agonists are associated with high cost and injectable administration.

These limitations highlight the importance of searching for alternative biologically active compounds of natural origin [10].

Oligopeptides as Promising Bioactive Compounds

Oligopeptides are short chains of amino acids, typically consisting of 2 to 20 amino acid residues and having a molecular weight of approximately 200–2000 Da. Their biological activity depends on chain length, amino acid composition, sequence, and spatial configuration. Due to their small size, oligopeptides are characterized by high bioavailability, relative stability, and a wide range of pharmacological effects [11–13].

The most significant properties of oligopeptides include:

antioxidant activity;

antidiabetic effects;

antihypertensive action;

immunomodulatory activity;

reparative and regenerative properties.

Oligopeptides are obtained from various natural sources, including milk proteins, fish, plant proteins, and insects. In recent years, particular attention has been paid to insects as environmentally safe and biologically valuable sources of peptides. Among them, *Bombyx mori* is considered one of the most promising sources of bioactive compounds [14].

Biochemical Characteristics of *Bombyx mori* as a Source of Oligopeptides

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Bombyx mori (silkworm) is a biological organism whose materials contain significant amounts of proteins, lipids, carbohydrates, amino acids, and minerals. The silkworm cocoon mainly consists of fibroin and sericin. Fibroin is rich in glycine, alanine, and serine, whereas sericin is a water-soluble glycoprotein with pronounced biological activity. This amino acid profile makes silkworm proteins a valuable raw material for obtaining oligopeptides with pharmacological potential.

To obtain oligopeptides from *Bombyx mori* proteins, enzymatic hydrolysis is commonly used with enzymes such as Alcalase, trypsin, papain, pepsin, and Protamex. The process is carried out under mild conditions, which helps preserve the biological activity of the resulting peptides. After hydrolysis, ultrafiltration and lyophilization are performed, resulting in low-molecular-weight fractions with pronounced pharmacological activity. The most promising are short peptides containing 1–8 amino acid residues [15–16].

Pharmacological Activity of *Bombyx mori* Oligopeptides

Oligopeptides derived from silkworm proteins exhibit multifactorial biological activity. The literature describes their antioxidant, anti-inflammatory, regenerative, anti-aging, and metabolic effects. Of particular interest is their ability to influence carbohydrate metabolism and reduce hyperglycemia [17].

Antioxidant Activity

Bombyx mori oligopeptides are capable of neutralizing free radicals, inhibiting lipid peroxidation, and increasing the activity of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. This is particularly important because oxidative stress is one of the key mechanisms underlying β-cell damage and the development of insulin resistance in diabetes [18].

Regenerative and Cytoprotective Effects

Sericin peptides stimulate fibroblast proliferation, enhance angiogenesis, and promote tissue healing. These properties are potentially significant for the correction of diabetic complications, including delayed wound healing and microangiopathies [19].

Metabolic and Hypoglycemic Effects

The most significant pharmacological property of *Bombyx mori* peptides is their ability to modulate metabolic processes. Preclinical studies have shown that they improve glucose tolerance, increase insulin sensitivity, reduce fasting and postprandial blood glucose levels, and positively affect lipid profiles [14–18]. In several studies, blood glucose reduction reached 15–30%.

Possible Mechanisms of Hypoglycemic Action

The hypoglycemic activity of compounds contained in oligopeptides derived from *Bombyx mori* is realized through several interrelated mechanisms.

1. Inhibition of α-Glucosidase and α-Amylase

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Silkworm-derived peptides and proteolytic hydrolysates are capable of inhibiting intestinal enzymes such as α-glucosidase and α-amylase, thereby slowing carbohydrate digestion and subsequent glucose absorption. This contributes to the reduction of postprandial hyperglycemia.

2. Inhibition of DPP-4

Certain peptide fractions have demonstrated the ability to inhibit dipeptidyl peptidase-4 (DPP-4), which may lead to increased levels of endogenous GLP-1 and, consequently, enhanced insulin secretion. Low-molecular-weight dipeptides and tripeptides are considered particularly active in this regard.

3. Activation of the IRS-1/PI3K/Akt Pathway and GLUT4 Expression

Bombyx mori oligopeptides may improve insulin signaling by activating the IRS-1/PI3K/Akt pathway and increasing the expression of GLUT4. This enhances glucose uptake in muscle and adipose tissues, improving glucose utilization and reducing hyperglycemia.

4. Activation of AMPK and Regulation of Energy Metabolism

Peptides can activate AMP-activated protein kinase (AMPK), one of the key regulators of cellular energy metabolism. This is associated with suppression of hepatic gluconeogenesis, increased lipid oxidation, and overall improvement of the metabolic profile.

5. Antioxidant Protection of β-Cells

By increasing the activity of antioxidant enzymes and reducing the levels of reactive oxygen species, these peptides decrease apoptosis of pancreatic β-cells, thereby supporting insulin secretion [19–21].

Preclinical Data and Limitations

Numerous studies described in the literature have been conducted using streptozotocin- and alloxan-induced diabetic models, in which *Bombyx mori* materials demonstrated significant reductions in blood glucose levels, improvements in lipid profiles, and decreased oxidative stress. However, most of these data have been obtained from **in vitro experiments and animal models** [13–14].

It should be emphasized that results obtained under laboratory conditions cannot always be directly extrapolated to humans. The observed effects depend on multiple factors, including the method of hydrolysis, peptide composition, molecular weight, dosage, bioavailability, and stability of peptides in the gastrointestinal tract.

Furthermore, clinical studies in humans remain extremely limited. Therefore, despite promising findings, the application of these compounds in clinical practice is still premature and requires further investigation [21–23].

Future Perspectives

Oligopeptides derived from *Bombyx mori* represent a promising class of natural compounds for the development of new antidiabetic drugs, dietary supplements, and functional food

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products. Their advantages include natural origin, multimodal mechanisms of action, potential safety, and the ability to influence multiple pathogenetic pathways of diabetes mellitus [24–26].

Particular interest lies in the possibility of combining hypoglycemic, antioxidant, and hypolipidemic effects within a single bioactive substance. This makes these peptides promising not only for the correction of hyperglycemia but also for the prevention of diabetic complications.

However, further progress in this field requires standardization of peptide isolation methods, in-depth investigation of molecular mechanisms, toxicological evaluation, pharmacokinetic studies, and large-scale clinical trials [27–29].

Conclusion

Thus, compounds contained in oligopeptides derived from *Bombyx mori* possess significant hypoglycemic and metabolic potential. Their effects are mediated through inhibition of α-glucosidase, α-amylase, and DPP-4, activation of AMPK and IRS-1/PI3K/Akt signaling pathways, upregulation of GLUT4 expression, reduction of oxidative stress, and protection of pancreatic β-cells.

The combination of these mechanisms makes these compounds promising candidates for the development of new strategies for the prevention and treatment of diabetes mellitus. However, current evidence is largely limited to preclinical studies, necessitating further experimental and clinical validation.

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