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Molecular mechanisms of novel peptides from silkworm pupae that inhibit α-glucosidase

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ABSTRACT

The objectives of this study were to identify peptides that inhibit α-glucosidase using a quantitative structure-activity relationship (QSAR) screening method and a database of silkworm peptides. This study compared the docking characteristics of several peptides with high inhibitory activity against α-glucosidase and summarized the molecular mechanisms by which the silkworm peptides affected α-glucosidase. Four peptides that strongly inhibited α-glucosidase were obtained: Gln-Pro-Gly-Arg with IC_{50} at 65.8 μmol/L, Ser-Gln-Ser-Pro-Ala at 20 μmol/L, Gln-Pro-Pro-Thr at 560 μmol/L and Asn-Ser-Pro-Arg at 205 μmol/L. Studies docking the peptides to the active site of α-glucosidase (PDB ID: 2QMJ) showed that a common characteristic was Lys776 in 2QMJ, which could be a critical target for α-glucosidase trapping of inhibitory peptides. The results revealed that the four peptides, especially Ser-Gln-Ser-Pro-Ala, could be potential drugs for treating diabetes.

1. Introduction

Diabetes is a group of metabolic diseases. The World Health Organization estimates that 346 million people have diabetes and this number will double by 2030. The predicted increase is mainly in type 2 diabetes [4]. In addition to treatment with drugs such as acarbose and metformin, nutraceuticals and functional foods are a way to inhibit hyperglycemia. Since α-glucosidase and a-amylase are key enzymes in insulin adjustment, inhibition of these enzymes is a therapeutic target for retarding glucose absorption and suppressing postprandial hyperglycemia. Diabetes can be controlled by α-glucosidase inhibitors that suppress carbohydrate digestion [1]. However, α-glucosidase inhibitors such as acarbose and metformin can cause side effects such as flatulence (78% of patients) and diarrhea (14% of patients). Therefore, folk medicine and functional foods, especially functional peptides, have attracted research interest [15].

We reported that hydrolysates of silkworm pupae protein have angiotensin-I-converting enzyme (ACE) inhibitory activity [13]. In the *Compendium of* Materia Medica, Ming Dynasty medical scientist Li Shizhen reported that silkworms can be used to treat diabetes. Zhao reported that silkworm-egg powder affected SOD and SOD mRNA expression in diabetic,mice [16]. However, we do not know the silkworm components with these functions. Based on our research on peptides from silkworm pupae proteins with multiple functions [13]. we hypothesized that peptides in silkworm pupae protein hydrolysates would inhibit α-glucosidase.

Most α-glucosidase inhibitors are found through high-throughput screening or structure modification. However, the structures of many inhibitors are complex, and the characteristics of their structure and the relationships between their structures and activities are not clear. These issues create difficulties in discovering and researching α-glucosidase inhibitors. We aimed to identify peptides that inhibit α-glucosidase using a quantitative structure activity relationship (QSAR) screening method and a silkworm peptide database. We compared the docking characteristics of several peptides with inhibitory activity against α-glucosidase, and summarized the molecular mechanisms by which silkworm peptides affected α-glucosidase.

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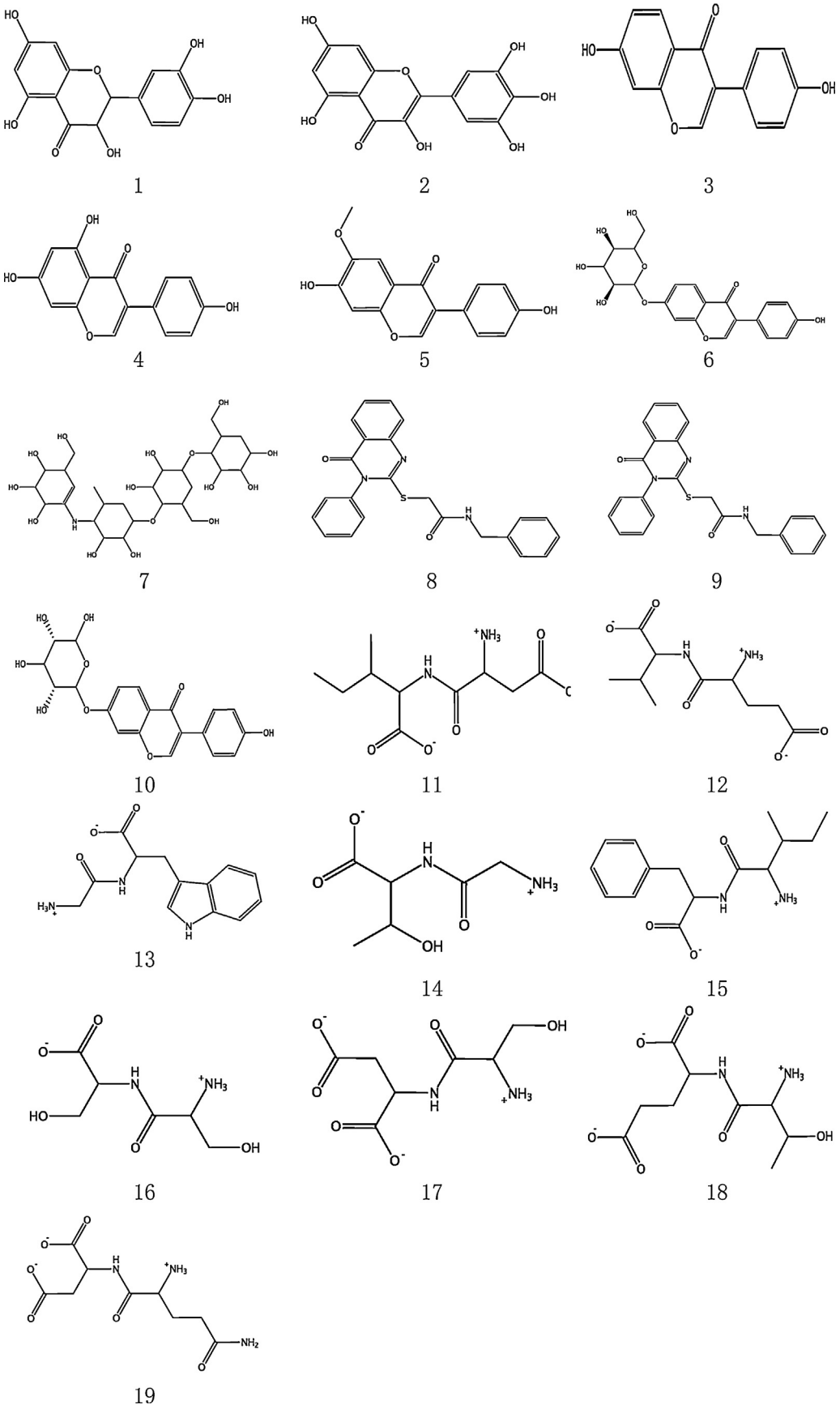

Fig. 1. Two-dimensional structures of compounds in the training set. There are 19 a-glucosidase inhibitors including 9 peptides (No. 11–19) and 2 compounds (No. 8–9) and 8 medicines (No. 1–7,and No.10).