

Prospect of Marine Bioactive Peptides as DPP4 Inhibitor



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Abstract

Dipeptidyl peptidase 4 (DPP4) is an enzyme that plays important role in metabolism and due to its exacerbating role in glucose metabolism, it is essential to inhibit its function to ameliorate Type 2 Diabetes Mellitus (T2DM). Vildagliptin, sitagliptin and some other drugs are being used worldwide. As a new source, marine derived bioactive peptide having DPP4 inhibitory effect would have a promising role to control its regulatory effect on disease manifestation.

Keywords: DPP4 inhibition; Marine derived origin; Marine bioactive peptide

Abbreviations: DPP4: Dipeptidyl Peptidase 4; T2DM: Type 2 Diabetes Mellitus; GIP: Glucose-Dependent Insulinotropic Polypeptide; GLP1: Glucagon-like Peptide-1; ROS: Reactive Oxygen Species, RAGE: Receptor for Advanced Glycation End Products; FDA: Food and Drug Administration; APCs: Antigen-Presenting Cells

Introduction

Dipeptidyl peptidase 4 (DPP4)/CD26 is a serine exopeptidase enzyme that cleaves the N-terminal dipeptides with proline or alanine amino acids from the N-termini of polypeptides leading to regulate the activities of a number of peptide hormones and chemokines. It is known that DPP4 is responsible for the degradation of several incretins such as glucagon-like peptide-1 (GLP1), glucose-dependent insulinotropic polypeptide (GIP), thus regulating the blood glucose level by sensitizing insulin secretion [1]. Upon T cell stimulation, DPP4 expression is markedly up-regulated along with its increased release in soluble form in the blood, which also suggests DPP4 as a T cell co-stimulatory molecule that exerts its effect through binding to adenosine deaminase and interacting with T cell receptor complex. Bunch of studies suggests that DPP4 is a novel adipokine, which is correlated with the amount of adipose tissue inflammation, and insulin resistance as well. Several reports suggest that DPP4 is also released in soluble form exerts lots of cellular effects such as stimulation of reactive oxygen species (ROS), induction of inflammation in smooth muscle cells. Generally, soluble DPP4 interacts to cell surface receptor(s) and executes numerous effects such as activation of T cells, induction of smooth muscle cells inflammation, stimulation of insulin resistance in various tissues, augmentation of CD86 in antigen-presenting cells (APCs), enhancement of smooth muscle

cell proliferation, stimulation of reactive oxygen species (ROS) generation and induction of receptor for advanced glycation end products (RAGE) gene expression, and so on [2].

To manage the excessive adverse effects of DPP4 at the cellular level, scientists are suggesting some pharmacological intervention as a drug and in this case vildagliptin, sitagliptin, approved by the Food and Drug Administration (FDA), are most widely used. Beside these two drugs, saxagliptin and alogliptin are also being suggested [3]. Most of the cases these drugs are approved to be used in a combinatorial therapy like in combination with metformin, sulphonylureas, thiazolidinediones etc. As an alternative source of DPP4 inhibitor, marine derived sources would have a great potential in therapy [4] and more specifically marine derived bioactive peptides production would be one of the areas of utmost interest in DPP4 inhibitor activity. It is known that ficin digested gliadins-derived peptides possess strong dipeptidyl peptidase 4 inhibitory activity as well as antihypertensive and antioxidant activities. As a functional food or dietary supplement, marine peptides derived from seaweeds, sponges, fish-skin, fish-bones, fish-scales, mollusks, crustaceans and marine byproducts including substandard muscles, viscera and trimmings would have a great potential targeting DPP4 inhibition. It is known that Gly-Pro-Ala peptide works as a DPP4 inhibitor, which has a great

relevance as a natural source for Type II diabetes mellitus (T2DM) management in both *in vitro* and *in vivo* through incretin effect. In one study using RubisCO of *Halophila stipulacea*, a sea grass, lots of bioactive peptides were found by using chymotripsine digestion, which showed strong DPP4 inhibitory activities such as GL, PL, GF, KY, RL, TY, VF. In the same species, trypsin digestion gives DPP4 inhibitory activity with the bioactive peptide sequence of DF. Proteinase K digestion also gives DPP4 inhibitory function with TP, SP, KP, EP, QP, AY, EY, GV, HI, QV, RI, TP and so on. In line with these, pancreatic elastase digestion provides several important bioactive peptide sequences having DPP4 inhibitory role such as RA, PL, WT, ET, KG, KT, NV, RG, and so on [5]. Thus, marine source as a bioactive peptide would have huge potential.

The recent age, blue economy emerged a lot of potential and various countries are now focusing on exploring the marine resources in their coastal region. Various pharmaceutical companies are also searching for new sources of secondary metabolites and as a DPP4 inhibitory agent, bioactive peptide

from marine origin would open a new window to explore this field.

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