Anti-diabetic effects of seaweeds: potential mechanisms

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Diabetes mellitus

Marine algae

* Unsaturated fatty acids
* Dietary Fibers
* α-Glucosidase inhibitors
* Glucose uptake in skeletal muscle
* Anti-oxidant effects
* Anti-Inflammatory effects

Conclusion
Diabetes mellitus

• Chronic metabolic disease

• Hyperglycemia

• Type I DM
• Type II DM

• Prevalence:
  ▫ 2000: 2.8%: 171 million
  ▫ 2030: 4.4%: 370 million
• Increase risk of
  ▫ Hypertension
  ▫ Microvascular complications
    • Retinopathy
    • Nephropathy
    • Neuropathy
  ▫ Macrovascular complications
    • Cardiovascular diseases
    • Stroke
• T2DM: reduce life expectancy due to these co-morbidities
• Effective control of blood glucose levels
  ▫ Preventing or reversing diabetic complications
  ▫ Improving the quality of life
Intestines absorb glucose after a meal. Glucose enters the bloodstream. Increasing glucose level signals the pancreas to secrete insulin. Insulin causes liver, skeletal muscle, and other tissues to take up more glucose, restoring homeostasis.

Pancreas responds to high glucose level by secreting insulin. Insulin causes liver, skeletal muscle, and other tissues to take up more glucose, restoring homeostasis.
Drugs for diabetes mellitus

- Insulins
  - Rapid, short-acting (lispro, regular)
  - Intermediate-acting (NPH, lente)
  - Slow, long-acting (glargine)
- Noninsulin antidiabetic drugs
  - Insulin secretagogues (glipizide)
  - Biguanides (metformin)
  - Alpha-glucosidase inhibitors (acarbose)
  - Thiazolidinediones (pioglitazone)
  - Amylin analogs (pramlintide)
  - Incretin modulators
  - SGLT2 inhibitors (canagliflozin)
  - GLP-1 analog (exenatide)
  - DPP-4 inhibitor (sitagliptin)
Action sites of oral hypoglycemic agents and mechanisms of lowering blood glucose in type 2 diabetes mellitus.
Marine algae
Seaweed consumption & diabetes

- Coastal communities in Asia
- Japanese: 5.3 g/day
- High consumption of seaweed in daily diet has been associated with lower risk of
  - Cardiovascular disease
  - Hyperlipidaemia
  - Breast cancer
Seaweed consumption & diabetes

• Dietary consumption of *Porphyra yezoensis* and *Undaria pinnatifida* was associated with low incidence of diabetes in Korean men

• The consumption of commercial blend of *Ascophyllum nodosum* and *Fucus vesiculosus* was associated with improved insulin regulation and sensitivity

• Consumption of mekabu (sporophylls of *Undaria pinnatifida*) with a white rice-based breakfast by healthy volunteers demonstrated a reduction of post-prandial glucose concentration
Unsaturated fatty acids

- Monounsaturated fatty acids (MUFA)
- Polyunsaturated Fatty Acids (PUFA)

- Improve insulin sensitivity in healthy and glucose-intolerant subjects
- Promoting glucose uptake by up-regulating glucose transporter type 1 (GLUT1) and type 4 (GLUT4) in the cell membrane
- Cytoprotective effects on pancreatic β-cells
Dietary Fibers

• High intakes of dietary fiber: reduced incidence of T2DM
  – 30 g/day for healthy individuals
  – 50 g/day for diabetic patients

• Prolong gastric clearance rate: increased satiety and reduction of food intake: weight loss
Many seaweed species contain similar or higher total fiber content compared with their terrestrial counterparts:

- *Himanthalia elongata*,
- *Ascophyllum nodosum*,
- *Laminaria digitata*
- *Palmaria palmata*

Higher percentage of total dietary fiber and lower soluble carbohydrate (g/100 g weight) compared with brown rice and bananas.
α-Glucosidase inhibitors

• α-amylase and α-glucosidase: Starch digestion

• Postprandial hyperglycemia lowering effect

• Crude extract
  – Caulerpa racemosa
  – Spatoglossum Schroederi
  – Halimeda macroloba
  – Padina sulcata
  – Sargassum binderi
  – Turbinaria conoides
  – Odonthalia corymbifera
  – Ascophyllum nodosum
  – Ecklonia cava
A) Oligosaccharides
  Polysaccharides

  Alpha-glucoside

  Monosaccharides

  Absorbed

B) Oligosaccharides
  Polysaccharides

  Alpha-glucoside

  Acarbose

  Competitive inhibition

  Absorbed

  Monosaccharides

  Postprandial hyperglycaemia

Source: Br J Cardiol (c) 2011 Medinews (Cardiology) Limited
Phlorotannins

• Ecklonia cava
  – Fucodiphloroethol G,
  – Dieckol
  – 6,6’-bieckol
  – 7-phloroeckol
  – Phlorofucofuroeckol

• Ecklonia stolonifera and Eisenia bicyclis
  – Phloroglucinol
  – Dioxinodehydroeckol

• Ishige okamurae
  – Diphlorethohydroxycarmalol (DPHC)

• Based on IC$_{50}$: more effective than acarbose
Hydroxyl groups: perform a crucial function in promoting inhibitory activity: bind to the active or binding sites of the enzymes, resulting in the inhibition of enzyme activity.
Dieckol, Diphlorethohydroxycarmalol (DPHC)
- Streptozotocin-induced diabetic and normal mice
  - The increase in postprandial blood glucose levels was suppressed

12-week supplementation with dieckol-rich extract (1500 mg/day) from *Ecklonia cava* in a randomized, double-blind, placebo-controlled clinical trial involving 80 pre-diabetic individuals
- significant reduction of insulin resistance and post-prandial hyperglycaemia

Phlorotannins: may prove useful as an effective natural anti-diabetic compound.
The skeletal muscle: major role in the regulation of energy balance and is the primary tissue for glucose uptake

- glucose uptake by skeletal muscle accounts for >70% of the glucose removal from serum in humans

- Insulin signaling pathway through phosphatidylinositol-3 kinase (PI3-K) and Akt activity. Activation of PI3-K and Akt promotes glucose transporter 4 (Glut4) translocation from an intracellular pool to the plasma membrane

- 5′ adenosine monophosphate (AMP)-activated protein kinase (AMPK).
FIGURE 1 - Mechanisms evolved in the acute exercise-induced glucose transport. (Hayashi, Wojtaszewski, Goodyear, 1997; Zierath, 2002).
• Polyphenol-rich extract of the brown alga Ecklonia. cava
  – Activates both AMPK and PI3-K/Akt signaling in C2C12 skeletal muscle cells
• Dieckol isolated from E. cava:
  – Increases of glucose uptake in differentiated muscle cells
  – Glut4 translocation to the plasma membrane of L6 myotubes was markedly increased possibly through the activation of PI3-K/Akt signaling pathway
• Octaphloarethol A (OPA) (Ishige foliacea)
  – Increased glucose uptake in differentiated L6 rat myoblast cells
  – Increases Glut4-mediated glucose uptake by activating PI3-K/Akt and the AMPK signaling pathway
Protein tyrosine phosphatase 1B (PTP 1B)

- Cytoplasmic surface of the endoplasmic reticulum in classical insulin-targeted tissues such as muscle, fat and liver
- Negative regulator of insulin signaling and plays a key role in developing insulin resistance
- Inhibiting PTP 1B may be a potential therapeutic strategy for treating type-2 diabetes mellitus
• Phlorotannins isolated from edible brown seaweed *Ecklonia stolonifera and Eisenia bicyclis*
  – phloroglucinol, dioxinodehydroeckol, eckol, phlorofucofuroeckol A, dieckol, and 7-phloroeckol
• Bromophenol derivatives isolated from red seaweed *Rhodomela confervoides, Symphylocladia latiuscula, Laurencia similis*
• Potent inhibitors protein tyrosine phosphatase 1B
• Potential therapeutic candidate for the treatment of insulin resistance and type 2 diabetes
Anti-oxidant and Anti-Inflammatory effects

- Hyperglycaemia: a stressful condition for pancreatic β-cells and other insulin-sensitive cells including adipose tissues
  - Secretion of pro-inflammatory cytokines
  - Increases the risk of insulin resistance and β-cell failure

- Hyperglycemia: glucose autooxidation
  - Reactive oxygen species (ROS), nitric oxide (NO), peroxynitrite (ONOO)
  - Nephropathy, retinopathy, and neuropathy, endothelial cell dysfunctions
- Ecklonia stolonifera
- Ascophyllum nodosum
- Ecklonia maxima
- Ecklonia cava
- Ishige foliacea
- Undaria pinnatifida
- Saccharina japonica
- Ulva lactuca

- Suppress lipid peroxidation and oxidative stress
  - free-radical scavenging activity: DPPH assay
  - glutathione peroxidase (GSH-px), catalase (CAT) and superoxide dismutase (SOD)
  - Malondialdehyde, thiobarbituric acid reactive substances (TBARS)
- **Undaria pinnatifida**
- **Ulva linza**
- **Fucoxanthin**

  - Reduced the mRNA expression of MCP-1, PAI-1, IL-6 and TNF-α in white adipose tissue of diabetic KK-Ay mice

  - Reduced iNOS and COX-2 mRNA over-expression in RAW264.7 macrophage-like cells, as well as reduction of MCP-1 and IL-6 mRNA over-expression in adipocytes *in vitro*

  - Fucoidan from *U. pinnatifida* also reduced the expression of MCP-1, PAI- and TNF-α during adipogenesis in 3T3-L1 cells *in vitro*
• Dieckol and DPHC

• High glucose induced oxidative stress: human umbilical vein endothelial cell damage

  ▫ Protect the cells against the oxidative stress by reducing ROS generation and inhibiting the production of iNOS and COX-2, and by reducing NF-κB activation
Conclusion

• Seaweed and seaweed-derived bioactive compounds
  – Huge potential to be employed in T2DM management

• Dietary intake
• Supplements
• Purified pharmacological agents
Thanks for your attention