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Characterization of seaweed hypoglycemic property with integration of virtual screening for identification of bioactive compounds

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ABSTRACT

Seaweeds have been studied extensively for their nutritional values but their potential nutraceutical application remained underutilized due to uncharacterized bioactive compounds. Here we demonstrated that water extracts of *Kappaphycus*, *Halimeda*, *Padina* and *Sargassum* were able to improve insulin resistance, reduced hyperglycemia and protect liver and pancreatic tissue from HFD-induced damage in mice, with both *Padina* and *Sargasssum* displayed more significant results than the other two seaweeds. A list of potential bioactive compounds was then composed by virtual screening of 276 compounds detected by LC-MS on selected *Padina* fractions using molecular docking by Surflex-Dock. Further analysis determined punicate as the most potent bioactive compound that inhibits both glucosidase and dipeptidyl-peptidase-4 enzymes. In conclusion, we discovered novel in vivo hypoglycemic activity in *Halimeda* and several potential α-glucosidase and DPP-4 inhibitors in *Padina* via virtual screening, demonstrating the efficacy of molecular docking to facilitate discovery of novel bioactive compounds.

1. Introduction

Studies have repeatedly demonstrated the important role of diet towards human health, with growing evidence of dietary small bioactive molecules influencing various metabolic pathways and immune systems. Thus, utilizing dietary intervention to combat various chronic disease such as obesity, diabetes and even Parkinson's disease has garnered much research interest (Schwiertz et al., 2010).

Diabetes mellitus is a chronic metabolic disease that involved insufficient production of insulin (Type 1) or decreased insulin sensitivity (Type 2) (American Diabetes Association 2017). Globally, there are more than 422 million of diabetic sufferers with 1.6 million death directly attributed to the disease annually (WHO, 2018). Compared to Type 1, Type 2 diabetes mellitus (T2DM) poses the greater health problem as it accounts for nearly 90% of the global diabetes cases (Zheng, Ley, & Hu, 2018). The development of T2DM is closely linked to lifestyle, with obesity and physical inactivity being the largest risk factors (NIDDK, n.d.). One of the characteristics of T2DM is impaired glucose tolerance which is frequently associated with insulin resistance. The reduced response towards insulin would contribute to hyperglycemia, which leads to various health complications such as retinopathy, neuropathy and kidney failure (Bornfeldt & Tabas, 2011; Jellinger, 2009). Management of hyperglycemia has thus become a primary diabetes care strategy, targeting various phase and factors of glucose metabolism including α-glucosidase, dipeptidyl peptidase-4 (DPP-4), the incretin hormones gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) (Bonadonna, Borghi, Consoli, & Volpe, 2016; Derosa & Maffioli, 2012).

Seaweed are edible large marine algae and represent a rich source of bioactive compounds. Recent studies have discovered a large range of potential bioactivities by seaweed and its components including anti-hyperglycemia and anti-hyperlipidemia (Chin et al., 2015, 2019; Paxman et al., 2008; Sharifuddin, Chin, Lim, & Phang, 2015). However, due to the large number of compounds present in a sample, isolating the bioactive compound is both laborious and costly, typically involving a series fractionation and chromatography separation (Sasidharan, Chen, Saravanan, Sundram, & Yoga Latha, 2011). Hence, many reports of bioactivities are on consumption of whole plant or extracts without isolating and identifying the bioactive compound that were responsible for the bioactivities. This unclarity limits the applicability of the results

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