JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS
https://doi.org/10.1080/07391102.2023.2276889

Virtual screening, molecular docking, molecular dynamics, and MM-GBSA approaches identify prospective fructose-1,6-bisphosphatase inhibitors from pineapple for diabetes management

Md. Sanower Hossain[a], Miah Roney[b], Mohd Yusri Bin Mohd Yunus[a,c] and Jun Haslinda Shariffuddin[a,c]

[a]Centre for Sustainability of Mineral and Resource Recovery Technology (Pusat SMaRRT), Universiti Malaysia Pahang Al-Sultan Abdullah, Kuantan, Malaysia; [b]Faculty of Industrial Sciences and Technology, Universiti Malaysia Pahang Al-Sultan Abdullah, Kuantan, Malaysia; [c]Faculty of Chemical and Process Engineering Technology, Universiti Malaysia Pahang Al-Sultan Abdullah, Kuantan, Malaysia

Communicated by Ramaswamy H. Sarma

ABSTRACT

Diabetes affects millions globally and poses treatment challenges. Targeting the enzyme fructose-1,6-bisphosphatase (FBPase) in gluconeogenesis and exploring plant-based therapies offer potential solutions for improving diabetes management while supporting sustainability and medicinal advancements. Utilizing pineapple (*Ananas comosus* L. Merr.) waste as a source of drug precursors could be valuable for health and environmental care due to its medicinal benefits and abundant yearly biomass production. Therefore, this study conducted a virtual screening to identify potential natural compounds from pineapple that could inhibit FBPase activity. A total of 112 compounds were screened for drug-likeness and ADMET properties, and molecular docking simulations were performed on 20 selected compounds using blind docking. The lead compound, butane-2,3-diyl diacetate, was subjected to 100 ns MD simulations, revealing a binding energy of −5.4 kcal/mol comparable to metformin (−5.6 kcal/mol). The MD simulation also confirmed stable complexes with crucial hydrogen bonds. Glu20, Ala24, Thr27, Gly28, Glu29, Leu30, Val160, Met177, Asp178, and Cys179 were identified as key amino acids that stabilized the human liver FBPase-butane-2,3-diyl diacetate complex, while Tyr215 and Asp218 played a crucial role in the human liver FBPase-Metformin complex. Our study indicates that the lead compound has high intestinal solubility. Therefore, it would show rapid bloodstream distribution and effective action on the target protein, making butane-2,3-diyl diacetate a potential antidiabetic drug candidate. However, further investigations *in vitro*, preclinical, and clinical trials are required to thoroughly assess its efficacy and safety.

ARTICLE HISTORY
Received 24 May 2023
Accepted 22 October 2023

KEYWORDS
Ananas comosus; antidiabetic; docking; molecular dynamic; natural products; virtual screening

Introduction

Diabetes mellitus (DM), a group of metabolic disorders, is considered one of the fastest-growing chronic diseases in the world, affecting over 10% of adults globally (IDF, 2021). Experts predict that if no action is taken to address this trend, the number of people with diabetes could increase to around 643 million by 2030, representing about 11.3% of the global population. If current trends continue, this number could skyrocket to an astonishing 783 million, or 12.2% of the population, by 2045 (IDF, 2021). The situation is particularly severe in low- and middle-income countries, where over three-quarters of adults with diabetes reside. Moreover, many cases of diabetes go undiagnosed, implying that the actual prevalence of the disease may be higher than reported (IDF, 2021). Diabetes is also a significant health issue in Malaysia (Rahman et al., 2019), with an estimated 18.3% of adults affected by the disease in 2019, according to the National Diabetes Registry Report (Chandran et al., 2020). Therefore, individuals with diabetes need to manage their blood glucose levels to minimize the risk of diabetic complications.

Retarding glucose absorption during digestion has been a useful strategy for controlling blood glucose levels for many years, despite the limitations of certain medications (Bhandari et al., 2008; Gromova et al., 2021; Kato-Schwartz et al., 2020; Lalegani et al., 2018). Some medications, such as alpha-glucosidase inhibitors, act by inhibiting the enzymes responsible for the breakdown of carbohydrates in the small intestine. As a result, glucose absorption is slowed down, leading to a decrease in postprandial hyperglycemia. However, due to undigested carbohydrates in the lower gastrointestinal tract, alpha-glucosidase inhibitors can be associated with adverse gastrointestinal effects, including flatulence, diarrhea, and abdominal pain (Galasko, 2017; Ghosh & Collier, 2012; Khoo, 2017). These side effects are dose-dependent and can limit the tolerability of these medications in some patients (Khoo, 2017). Frequently, these adverse effects lead to the discontinuation of the treatment. So, there is an urgent need to develop novel alternative therapies.

CONTACT Jun Haslinda Shariffuddin junhaslinda@umpsa.edu.my

Supplemental data for this article can be accessed online at https://doi.org/10.1080/07391102.2023.2276889.