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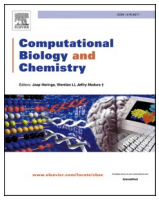

Comprehending the pharmacological mechanism of marine phenolic acids in bladder cancer therapy against matrix metalloproteinase 9 protein by integrated network pharmacology and in-silico approaches

Miah Roney [a,b], Md. Nazim Uddin [c], Mohd Fadhlizil Fasihi Mohd Aluwi [a,b,*]

[a] Faculty of Industrial Sciences and Technology, Universiti Malaysia Pahang Al-Sultan Abdullah, Lebuhraya Persiaran Tun Khalil Yaakob, Kuantan, Pahang, Malaysia
[b] Centre for Bio-aromatic Research, Universiti Malaysia Pahang Al-Sultan Abdullah, Lebuhraya Persiaran Tun Khalil Yaakob, Kuantan, Pahang, Malaysia
[c] Institute of Food Science and Technology, Bangladesh Council of Scientific and Industrial Research, Dhaka 1205, Bangladesh

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ABSTRACT

Bladder cancer (BC) is the 10th most common tumour with a high incidence and recurrence rate worldwide; however, the current therapies present limitations as, regularly, not all patients benefit from treatment. Therefore, the search for new, active marine phenolic acids with anti-tumour properties is imperative. In this study, we subjected marine phenolic acids to in silico investigations such as network pharmacology, molecular docking, and molecular dynamics simulation (MD) to identify a plausible pathway and the lead compound that inhibits BC. According to the network pharmacology analysis, eight hub genes (*PLAU, MMP2, ITGB3, MAPK1, PTPN11, ESR1, TLR4, MMP9*) were found and linked to the enrichment of hsa05205: proteoglycans in cancer, and four hub genes (*MMP1, MMP2, MAPK1, MMP9*) were involved in the enrichment of hsa05219: BC. Subsequently, molecular docking studies showed that the marine phenolic acids exhibit a strong binding affinity for the target protein, matrix metalloproteinase-9 (MPP9). Among these 14 marine phenolic acids, chicoric acid showed the highest binding affinity of −67.1445 kcal/mol and formed hydrogen bonds with the residues of Ala189, Gln227, Leu188, His226, Ala242, Arg249, Ala191, and Gly186 in the active site of the MPP9 protein. Then, molecular dynamics simulation revealed that chicoric acid formed a stable protein-ligand complex with RMSD and RMSF values of 0.72 nm and 0.53 nm, respectively. Furthermore, the PCA method was employed to understand the dynamical behaviour in the conformational space of MPP9 protein bound to chicoric acid, and the results showed the good conformational space behaviour of MPP9 protein. Moreover, chicoric acid showed a free binding energy value of −32.62 kcal/mol, which indicated it could be a BC inhibitor. Overall, chicoric acid demonstrated potential anti-BC activity through MPP9 protein inhibition.

1. Introduction

Cancer poses a significant global health burden, characterised by aberrant cell proliferation leading to mortality. Despite extensive research investment, precise disease delineation remains elusive, and annual diagnoses and fatalities underscore its severity. Approximately 14.1 million new cases, 8.2 million fatalities, or 14.6 % of all cancer-related deaths in humans, were reported worldwide in 2012 (excluding melanoma-related skin cancer). It is estimated that there will be 17 million cancer deaths annually and 26 million new cases of cancer by 2030 (Dai et al., 2016). Furthermore, there are now over 100 different forms of cancer, and the incidence rates are rising, indicating a concerning phenomenon (Dai et al., 2016). Among them, BC is the most prevalent cancer-associated death worldwide, accounting for 2.1 % of all cancer-related fatalities (Saginala et al., 2020). Globally, it ranks 10th in terms of frequency of cancer type; the most prevalent kind is urothelial carcinoma, accounting for over 90 % of cases (Jubber et al., 2023). According to their unique risk of progression, patients with non-muscle-invasive BC (NMIBC) are categorised as having low, intermediate, high, or very high risk (Zucca et al., 2024). Chemo-preventive treatments, though effective, are constrained by toxicity concerns. Oncogenesis typically originates from DNA mutations, compelling diverse therapeutic modalities like surgery, radiation, and chemotherapy (Speck-Planche et al., 2012a). However, limitations persist,

* Corresponding author at:Faculty of Industrial Sciences and Technology, Universiti Malaysia Pahang Al-Sultan Abdullah, Lebuhraya Persiaran Tun Khalil Yaakob, Kuantan, Pahang, Malaysia.
E-mail address: fasihi@umpsa.edu.my (M.F. Fasihi Mohd Aluwi).

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