UNIVERSITI TEKNOLOGI MARA

COMPUTER AIDED DRUG REPURPOSING FOR HUMAN BRCA1 ASSOCIATED PROTEIN 1 (BAP1)

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ABSTRACT

The BRCA1-associated protein 1 (BAP1) is a deubiquitinase (DUB) and act as a tumour suppressor. Mutations on the BAP1 has been linked to cancers, however, the molecular mechanism by which BAP1 regulate cancers are not fully understood. The absence of BAP1 crystal structure further hindered the progression in identifying its potential inhibitors. However, the BAP1's N-terminal UCH domain (BAP1N) is highly homologous to the UCHL5 template sequence. Thus, in this study, the structure of the BAP1N model was constructed through homology modeling based on the UCHL5 template sequence. The BAP1N model exhibited a good quality protein model as 87.7% of its amino acids residues are located in the most favoured regions of the Ramachandran plot. Molecular docking and molecular dynamics simulation (MDS) of the ubiquitin on the BAP1N model revealed the rearrangement of F228, F50, and H169 residues of the BAP1N switching its conformation into a productive state. Virtual screening results of potential BAP1 inhibitors against the FDA approved drugs shortlisted two potential inhibitors, which are FDA1065 (Flibanserin) and FDA755 (Risperdal). These compounds were further investigated via molecular MDS, followed by the molecular mechanics Generalized–Born surface area (MMGBSA) analysis on both inhibitors. The simulations showed that only the BAP1N-ubiquitin-FDA755 formed a stable complex and the FDA755 ligand maintained its position inside the active site of the BAP1 at the end of the simulation. It was observed that the presence of methyl group in FDA755 play an important role in stabilizing the BAP1-FDA755 complex. The MMGBSA calculation on both BAP1N-ubiquitin-FDA1065 and BAP1N-ubiquitin-FDA755 complexes showed both complexes were mainly contributed from non-polar terms and FDA755 showed the highest binding affinity with a total average binding energy of (-51.77 ± 3.49 kcal/mol). Thus, the FDA755 (Risperdal) and was suggested as the best BAP1N direct inhibitor. From this study the human BAP1N model was successfully generated using homology modeling technique and its potential inhibitor from the FDA approved drugs was successfully identified using molecular docking and molecular dynamics simulation. Thus, scientific communities will be able to use the BAP1N model for virtual screening against various large database of chemical compounds based on the information obtained in this study.

Keywords: BAP1, DUB, UCH, homology modeling, molecular docking, molecular dynamics simulation.

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This thesis is dedicated to my parents for their unwavering love and patience. This piece of victory is dedicated to both of you.

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CHAPTER ONE
INTRODUCTION

1.1 Introduction

The BRCA1-associated protein 1 (BAP1) is a multi-protein complex consisting of up to ten different protein subunits (Szczepanski & Wang, 2021). BAP1 functions as a tumour suppressor by acting as a deubiquitinase (DUB) that regulates cell division to ensure normal cell growth. Mutations on the BAP1 especially its N-terminal UCH domain (BAP1N) (Bhattacharya et al., 2015) and expression level were observed to affect tumorigenesis in different type of cancers (Qin et al., 2015; Scheuermann et al., 2010; Tsuboyama et al., 2022) including uveal melanoma (Harbour et al., 2010), mesothelioma (Cheung & Testa, 2017), clear-cell renal cell carcinoma (Pena-Llopis et al., 2012), and breast cancer (Shahriyari et al., 2019).

Even though various studies were conducted to identify potential BAP1 inhibitors, the molecular mechanism through which BAP1 regulate the cancer are not yet fully understood (Carbone et al., 2020). Moreover, the lack of BAP1's crystal structure in the PDB database greatly hampered the efforts in finding its potential inhibitors. A great number of efforts have been invested in finding BAP1 potential inhibitors through experimental methods, however, these methods were time consuming and expensive to conduct.

Computer Aided Drug Design (CADD) is a fast, reliable, and accurate in-silico methods that act as alternatives in drug exploration. Several types of drugs were successfully marketed to the public using these in-silico methods, proving the validity and advantage of these methods in yielding accurate results comparable to the conventional drug design methods. Therefore, this study aims to generate a three-dimensional (3D) protein model of human BAP1N using homology modeling as an alternative to construct a representation of the BAP1N structure.

Based on the generated protein model, potential inhibitors of BAP1N that directly inhibit its active site was explored using molecular docking and molecular dynamics simulation. Results from this study allowed the visualization of the BAP1N model constructed based on its homologs protein sequences, the identification of direct inhibitors of BAP1N and their binding properties inside the BAP1N active site.