UNIVERSITI TEKNOLOGI MARA

PREDICTION OF NOVEL ANGIOGENESIS INHIBITORS USING *IN SILICO* METHOD

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ABSTRACT

Angiogenesis plays in important role in tissue repair and could cause all kind of complications when its balance is disturbed. Cancer and angiogenesis is closely related and inhibiting angiogenesis in cancer is heavily studied. Humanized monoclonal antibody such as bevacizumab is one of many angiogenesis inhibitors available in the market. However, it is administered intravenously and the treatment can be very expensive. The purpose of this study is to build a computational model that first analyzes protein-ligand binding patterns of anti-angiogenesis drugs for the purpose of predicting a novel angiogenesis inhibitor. 12 different angiogenesis receptors studied and compounds associated with them were obtained from ChEMBL database and serves as the training set. 8 different prediction models were built, which were from the combination of different fingerprints (ECFP_4, FCFP_4, PubChem, MACCS) and machine learning algorithm (Naïve Bayes, Decision Tree). The combination of MACCS-Decision Tree performed the best, with a sensitivity and specificity values of 0.92 at rank 5. The MACCS-Decision Tree model was then subjected to external validation where 4 compounds; Shiraiachrome-A, 11,11'-dideoxyverticilin, Quercetin and TKI-31, obtained from scientific literature were tested. The model was able to predict the correct target for 3 of the compounds. This goes to show that the model can be used to discover novel anti-angiogenesis drugs. Future work should include the in vivo or in vitro validation of the *in silico* result.

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CHAPTER 1

INTRODUCTION

1.1 Introduction

According to the World Health Organisation (WHO), cancer arises from a single mutated cell that later metastasized into cancerous cells and develop tumour. In metastasis, cancer cells will travel from where it first started (primary cancer) via blood and lymphatic systems and form new metastatic tumours in other parts of the body. The transformation of a normal cell to a tumour cell is a multiple stage process.

From the World Cancer Report 2014, cancer is among the major causes of morbidity and mortality around the world, with approximately 14 million new cases and 8.2 million deaths in 2012. The number is projected to increase by 70% over the next twenty years.

There are various treatment options available in treating cancer and one known method is through inhibiting the angiogenesis process. Angiogenesis is the process of new blood vessels formation from a pre-existing blood vessel. It provides nutrients for the tumours to grow and later spread to other parts of the body. Currently, one of the widely-used angiogenesis inhibitors available in the market is bevacizumab, a humanized monoclonal antibody, which binds to VEGF (vascular endothelial growth factor) and stops the binding to VEGFR (VEGF receptor), marketed in the form of injection.