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IN SILICO DESIGN AND SYNTHESIS OF NOVEL FLAVONOID DERIVATIVES AS BIOAVAILABLE ANTICANCER AGENTS



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DERIVATIVES AS BIOAVAILABLE ANTICANCER AGENTS

AHMED BADRELDIN AHMED MAEBED



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2026





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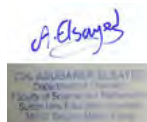
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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

'قُلْ لِّهِ يَ هَدَىٰ رَبِّي لِيَصْرَاطٍ مُّبِينٍ ۖ فَمِنْ أَقَامَ لِمَا هَدَىٰ رَبِّي ۖ وَمَا كَانَ مِنْ لِّمَنِ رَيْبٍ ۖ قُلْ إِنِّ صَلَّيْتُ
وَنَسَكَتِي وَمَخَّيَايَ وَمَهَلِّي لِلَّهِ رَبِّ الْعَالَمِينَ ۖ لَشَيْءٌ كَلَّهٖ وَبَالِكُ أَمْرَتْ وَلَئِذَا أَوَّلُ لِمَهْلِهِنَّ'

[العام: 161-163]

First, I want to thank Allah for his guidance and mercy as this work could not have been completed without his *Tawfik*. This belief arrived to us through *Rasol Allah* (sayedi Mohamed), therefore, I want to thank him and his family and his followers and their followers including my grandparents Sheikh Thabit Zeidan and Hajj Ahmed Maebed Zeidan, May Allah bestow his mercy on them all. Secondly, I want to thank Dr. Abu-Baker for his continuous support and his belief in me. I want to thank him as a supervisor, a great leader, a real scientist, a godfather and a true friend. He shared his great knowledge and experience with me and taught me everything in this field. May Allah bestow his mercy on his parents. I want to thank his wife for her kindness too. May Allah support them and their son Mohamed. Thirdly, I want to thank Dr. Saripah for her help and support throughout these two years. I hope Allah supports her husband and sons. I want to thank Dr. Yuhanis for her kindness and GRA position. I want to thank Mr. Ibrahim and all the lab assistants, and everyone who helped me. Finally, I want to thank my parents for their support throughout these two years and the rest of my life. I want to thank my whole family, my little sister Maryam, my nephews; Omar, Farida and Fayruz. And all my friends.

"وَمَتَّقِي لِإِلَّهِ لِّلَّهِ عَمِّيَّتٌ وَلِيَّهِ رُحْبٌ"





ABSTRACT

The objectives of this study were to review and perform a computational study on previously reported flavonoids as tubulin inhibitors and to design and synthesize new bioavailable flavonoids as anticancer agents targeting tubulin. The Molecular Operating Environment (MOE 2019.0102) software was used for molecular docking (MD) and QSAR studies of reported and newly designed flavonoids. The ADMET and bioavailability studies were performed using the pkCSM online server. New flavonoids were successfully prepared from commercially available hydroxy benzaldehydes and acetophenones using multistep chemical synthesis including alkylation, Claisen Schmidt condensation and cyclization reactions. All intermediates and new flavonoids were purified using silica gel column chromatography, and their chemical structures were confirmed using NMR and LC-MS spectral analysis. The results of this study illustrated that only 14 flavonoids have reported IC_{50} as tubulin polymerization inhibitors and the MD study showed their binding affinity to the colchicine binding site and identified their important interactions. The QSAR study illustrated the relationship between flavonoids activity and their hydrophobicity. The ADMET study also supports the importance of hydrophobicity to enhance flavonoids bioavailability. The design of new hydrophobic flavonoids was promising to improve tubulin inhibitory activity and bioavailability. For further investigations, it was necessary to synthesize the newly designed flavonoids. The spectroscopic techniques identified and confirmed the chemical structures of 20 newly synthesized flavonoids. In conclusion, twenty new flavonoids were designed and synthesized based on various computational studies to develop active and bioavailable tubulin inhibitors for further biological examinations. This study's impact on cancer research is expected to reintroduce flavonoids as anticancer tubulin inhibitors.





DALAM REKA BENTUK SILIKO DAN SINTESIS TERBITAN FLAVONOID NOVEL SEBAGAI EJEN ANTIKANSER BIO TERSEDIA

ABSTRAK

Objektif kajian ini adalah untuk mengkaji dan melaksanakan kajian pengkomputeran terhadap flavonoid yang telah dilaporkan sebagai perencat tubulin, serta mereka bentuk dan mensintesis flavonoid baharu yang tersedia ada secara bio sebagai agen antikanser yang menyasarkan tubulin. Perisian *Molecular Operating Environment* (MOE 2019.0102) telah digunakan untuk kajian dok molekul (MD) dan QSAR bagi flavonoid yang telah dilaporkan dan yang baharu direka bentuk. Kajian ADMET dan ketersediaan bio dilakukan menggunakan pelayan dalam talian pkCSM. Flavonoid baharu telah berjaya disediakan daripada hidroksi benzaldehid dan asetofenon yang diperoleh secara komersial menggunakan sintesis kimia berbilang langkah termasuk tindak balas pengalkilan, kondensasi Claisen Schmidt dan pensiklikan. Semua perantara dan flavonoid baharu telah dimurnikan menggunakan kromatografi turus gel silika, dan struktur kimianya disahkan menggunakan analisis spektrum NMR dan LC-MS. Hasil kajian menunjukkan bahawa hanya 14 flavonoid yang dilaporkan mempunyai nilai IC₅₀ sebagai perencat pempolimeran tubulin, dan kajian MD menunjukkan kekuatan pengikatan mereka pada tapak kolkisin dan mengenal pasti interaksi pentingnya. Kajian QSAR pula menggambarkan hubungan antara aktiviti flavonoid dan sifat hidrofobiknya. Kajian ADMET turut menyokong kepentingan hidrofobisiti untuk meningkatkan ketersediaan bio flavonoid. Reka bentuk flavonoid hidrofobik baharu menunjukkan potensi dalam memperbaiki aktiviti perencatan tubulin dan ketersediaan bionya. Untuk kajian lanjutan, adalah perlu untuk mensintesis flavonoid baharu yang direka bentuk ini. Teknik spektroskopi telah mengenal pasti dan mengesahkan struktur kimia bagi 20 flavonoid baharu yang telah disintesis. Kesimpulannya, sebanyak 20 flavonoid baharu telah direka bentuk dan disintesis berdasarkan pelbagai kajian pengkomputeran untuk membangunkan perencat tubulin yang aktif dan tersedia ada secara bio bagi pemeriksaan biologi selanjutnya. Impak kajian ini terhadap penyelidikan kanser dijangka akan memperkenalkan semula flavonoid sebagai perencat tubulin antikanser.





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ABBREVIATIONS

ACN	Acetonitrile
ADMET	Absorption, Distribution, Metabolism, Excretion and Toxicity
CC	Column Chromatography
DMSO	Dimethyl sulfoxide
<i>d</i>	Doublet
<i>dd</i>	Doublet of doublet
<i>ddd</i>	Doublet of doublet of doublet
<i>dq</i>	Doublet of quartet
<i>g</i>	Gram
¹ H- ¹ H	¹ H- ¹ H Correlation Spectroscopy Hz
COSY	
H ₂ O ₂	Hydrogen peroxide
HSQC	Heteronuclear single quantum coherence
HMBC	Heteronuclear Multiple Bond Correlation
IC ₅₀	50% Inhibitory Concentration
<i>J</i>	Coupling constant
K ₂ CO ₃	Potassium Carbonate
LC-MS	Liquid Chromatography-Mass spectrum
<i>m</i>	Multiplet
M.D	Molecular Docking
MeO	Methoxyl





mg	Miligram
MHz	Megahertz
ml	Mililiter
m/z	Mass per charge
NaOH	Sodium Hydroxide
OBn	Benzoxyl
OEt	Ethoxyl
OHex	Hexoxyl
ppm	Part per million
<i>q</i>	Quartet
QSAR	Quantitative Structure Activity Relationship
<i>s</i>	Singlet
SAR	Structure Activity Requirments
TMS	Tetramethylsilane
TLC	Thin Layer Chromatography
<i>t</i>	Triplet
α	Alpha
β	Beta
π	Baye
°C	Degree celsius
δ	Delta





CHAPTER 1

INTRODUCTION



1.1 Research Background

Cancer is the second leading cause of mortality worldwide. It is a serious problem affecting the health of all human societies including Malaysia. In 2020, the number of new cases diagnosed with cancer in Malaysia was 48639 (about 0.15% of total population). On the other hand, 29530 cases have died in the same year according to world health organization (WHO). There are many types of cancer affecting Malaysian males and females, the most frequent types in males were lung cancer (17%), colorectal cancer (15.4%), prostate cancer (9.3%), nasopharynx cancer (7.4%), liver cancer (6.7%) and other types (44.2%) with a total number of 23052 cases. In females, breast





cancer is the most frequently type which presents about (32.9%), colorectal cancer comes as the second with (11.9%), ovarian cancer (7.2%), cervix uteri (6.8%), corpus uteri (5.5%) and other types (35.7%) with a total number of 25587 cases (Cabasag, 2022).

Mutations in genes sequences followed by changes in cell functions are responsible for cancer development. Gene mutations usually occur due to chemical substances, smoking, viruses, bacteria and radiation rays which all are considered carcinogenesis factors. In general, cancer disrupts cellular processes and results in the dysfunction of vital genes and suppressor genes triggers uncontrolled cells division leading to uncontrolled cell proliferation (Hassanpour and Dehghani, 2017). There are many strategies for cancer treatment. One of these strategies is chemotherapy which depends essentially on finding a specific target that affects cancer cells with no or minimal side effects on normal cells if possible. Researchers focus their efforts to discover selective targets on cancer cells and to discover new drugs. Many targets are reported as selective cancer targeting chemotherapy. For example, many kinases have been targeted for cancer chemotherapy research (El-Kardocy, 2020). DNA and RNA variable enzymes are one of the promising targets. However, in this study we will focus on tubulin as a promising target for cancer chemotherapy and specifically the colchicine binding site of the tubulin protein.

Microtubules are characteristic cytoskeletal structures that consist of the self-assembly of tubulin heterodimers (mostly α and β subunits). Microtubules responsible for different functions that include cell movement, vesicle transport, and chromosome





segregation during mitosis which makes it critical element in cell cycle and essential biological structure in the cell. Cytoskeletal subunits of microtubules are highly dynamic and capable of polymerizing, depolymerizing, and moving within the cell cytoplasm. Drugs which interfere with dynamic equilibrium of polymerization and depolymerization of microtubules are called tubulin interactors. Therefore, they are classified into two categories: tubulin stabilizing agents (inhibitors of depolymerization) and tubulin destabilizing agents (inhibitors of polymerization) which disturb the equilibrium process. Therefore, no microtubules will be available to produce mitotic spindles for cell division leading mostly to cell cycle arrest and cell apoptosis. Polymerization and depolymerization inhibitors are further classified according to their binding domains. There are various sites of actions where drugs bind to the tubulin causes inhibition of cell division. Basically, three main binding sites were reported: the colchicine binding site, the Vinca binding site and the Taxol binding site. Both colchicine and vinca binding sites are related to tubulin polymerization inhibitors while the Taxol binding site is related to tubulin depolymerization inhibitors (Uivarosi, 2019; Desai, 1998; Downing, 1998).

Colchicine (**1**) was extracted from the poisonous meadow saffron *Colchicum autumnale* L. and It has been used as an unapproved treatment for familial Mediterranean fever, gout, pericarditis and Behçet's disease for many years. In 2009, U.S. Food and Drug Administration (FDA) approved colchicine (**1**) as a monotherapy drug to treat familial Mediterranean fever and acute gout flares. The effect of colchicine (**1**) on mitosis inhibition and since cancer cells mitosis occur at a significantly overexpressed rate, this means that cancer cells are more susceptible to colchicine (**1**) cytotoxicity than normal cells. Therefore, colchicine (**1**) is also being investigated as an





anticancer drug. Colchicine (**1**) was found to target a specific binding site in tubulin. Colchicine active site is considered a promising target for tubulin inhibition. It is located between the α and β tubulin subunits (Figure 1.1). Moreover, studies suggest that the position of colchicine active site can be exploited to decrease drug resistance. However, the therapeutic value of colchicine (**1**) against cancer is restrained by its low therapeutic index which includes neutropenia, gastrointestinal upset, bone marrow damage and anemia. Therefore, colchicine (**1**) is used as a leading compound to discover promising drugs like combretastatin A-4 (**2**), podophyllotoxin (**3**) and chalcones (Slobodnick, 2015; McLoughlin, 2020; McKeage, 2010).

Flavonoids are natural products consisting of different classes and are produced by many types of plants, vegetables and fruits as secondary metabolites. They can also be synthesized according to different chemical methods (Estévez-Sarmiento, 2017). During the last three decades, flavonoids exhibited anti-inflammatory, antioxidant and anticancer activities. The anticancer potential of flavonoids refers mainly to tubulin polymerization inhibition in cancer cells leading to cell apoptosis (as centaureidin (**4**)) (Beutler, 1993) or in endothelial cells in the vascular that supply the tumor leading to vascular disrupting as in flavonoid acetic acid (**5**) (FAA), the first flavonoid was discovered as vascular disrupting agent (Touil, 2009). The phenyl benzopyrone (C6-C3-C6) basic structure of flavonoids is considered a promising skeleton that was found suitably fitted to the colchicine binding site (Beutler, 1998).

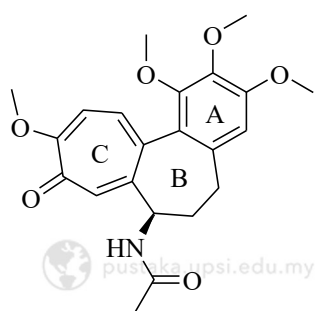
The current study includes the design, synthesis and evaluation of new flavonoid derivatives as ant-cancer agents targeting tubulin. The design of new flavonoid



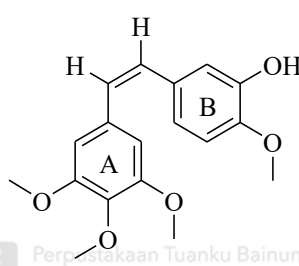
derivatives is based on a computational analysis of flavonoids that were reported as tubulin polymerization inhibitors. The design covers two main milestones: firstly, the flavonoids activity against tubulin polymerization and secondly, the enhancement of flavonoids bioavailability. Synthesis of newly designed flavonoids was performed using Claisen-Schmidt condensation reaction to synthesize chalcones followed by cyclization reaction to synthesize flavonoid analogues.

Figure 1.1

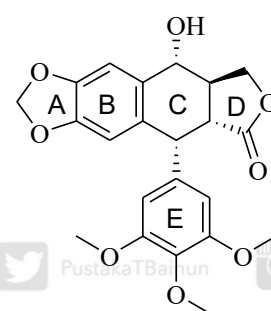
Colchicine-binding Site Inhibitors (CBS, 1-5) and CBS representation Between the Tubulin α (with Yellow Chain) and β (with Purple Chain) Dimers.



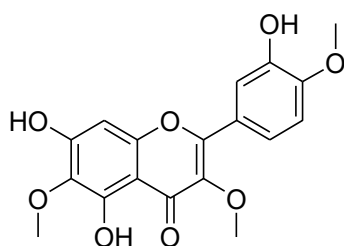
Colchicine (1)



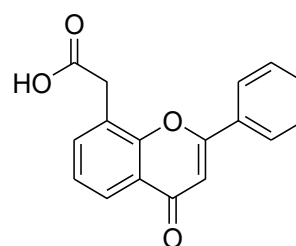
Combretastatin A-4 (2)



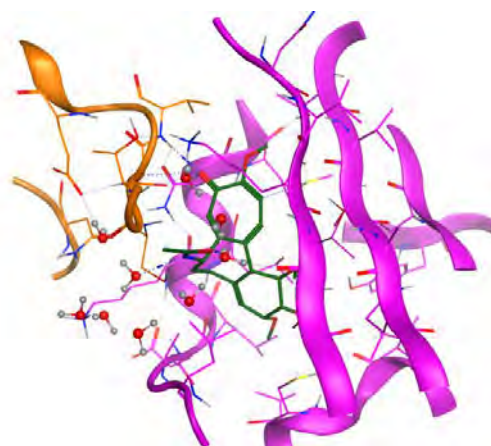
Podophyllotoxin (3)



Centaureidin (4)



Flavonoid acetic acid (FAA) (5)





1.2 Problem statement

Breast cancer is the most common cancer among women in Malaysia and worldwide. In 2020, it accounted for 8,418 new cases and 3,503 deaths according to the Malaysian National Cancer Registry (Cabasag, 2022). This represents 32.9% of all new women cancer cases. Tubulins are a group of proteins found at high levels in the cell cytoplasm which play a major role in many essential cellular processes such as mitosis, cellular movement, and segregation of chromosomes. Therefore, inhibition of tubulin leading to inhibition of cancer cell's many functions and cell death. Colchicine (**1**), a naturally derived compound, effectively prevents assembly of tubulin into microtubules but cannot be used as anticancer therapeutic due to its high toxicity. Interestingly, colchicine (**1**) binds to a tubulin site which is less susceptible to resistance and provides an attractive approach to target breast cancer with new therapeutics. Flavonoids and chalcones are natural metabolites found in various plants used in Asian traditional medicine and provide structurally related alternatives for colchicine (**1**) with better safety profile and promising anticancer activities through tubulin inhibition. There is a research gap regarding the design of synthetic flavonoids targeting the colchicine binding site of tubulins and their use as anticancer agents. The current proposal aims to fill this research gap through the design and synthesis of new flavonoids such as tubulin inhibitors and anticancer agents.



1.3 Objectives of the study

1. To study the quantitative structure-activity relationships (QSAR), bioavailability and molecular docking of previously reported flavonoids as tubulin polymerization inhibitors.
2. To design new flavonoid derivatives as tubulin inhibitors using computational methods.
3. To synthesize a new series of flavonoid derivatives

1.4 Significance of study



This study is focused on investigating the pharmacokinetics and pharmacodynamics of flavonoids such as tubulin polymerization inhibitors using different computational studies. It will introduce novel flavonoid derivatives which are expected to be more active and possess better bioavailability.

1.5 Scope of study

1. There are different studies which investigated chalcones and their behavior inside colchicine binding site and their bioavailability. Chalcones are precursors of



flavonoids, and we aim to shed light on flavonoids as tubulin polymerization inhibitors. Therefore, we are interested in investigating previously reported flavonoids and preparing a review collecting reported flavonoids having tubulin polymerization activities with a known biological method and reported IC₅₀. A computational study using the Molecular Operating Environment (MOE) software (including molecular docking study and QSAR study) and pkCSM online server (for ADMET study) will be performed for these reported flavonoids that showed tubulin polymerization inhibition activity.

- 2 After understanding flavonoids interactions with the colchicine binding site from the above-mentioned computational study, we aim to design novel derivatives of flavonoids using this computational study. A new series of flavonoids will be built using MOE software and their docking into the colchicine binding site of the tubulin will be investigated. The newly designed flavonoid's main goal is to enhance activity and bioavailability.
- 3 Newly designed flavonoids which achieve the highest binding scores (15 compounds) will be selected for synthesis according to a definite chemical scheme depending on suitable, easy and green chemistry to achieve one of the study goals.