UNIVERSITI TEKNOLOGI MARA

HIT TO LEAD: UNRAVELLING THE POTENTIAL OF FLAVONOIDS AS MULTI-SUBTYPES PHOSPHODIESTERASE (PDE) INHIBITORS

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Postgraduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Drug discovery is a lengthy process that requires a lot of resources and investment. Using computational approach, the time and the cost of drug development could be reduced. Drug candidates that fail to go into market due to unfavourable pharmacokinetic profiles and toxicity could be decreased. Chalcones, flavones, and flavanones are known to have various pharmacological activities including anti-inflammation. Many top leading causes of death are linked to inflammation-related diseases. Phosphodiesterase (PDE) specifically PDE4 is recognised as one of the emerging targets in inflammation which regulates cellular signalling through catalysing the degradation of cyclic nucleotides (cNMPs). Inhibiting PDE4B may increase the concentration of cNMPs and decrease the inflammatory mediators. However, the occurrence of adverse effects such as nausea and emesis have limited the usage of this inhibitor. Hence, the study aimed to identify multi-subtypes PDE inhibitors based on chalcone, flavone, and flavanone scaffolds using *in silico*, *in vitro,* and *in vivo* approaches. In this study, three different sources of chalcone, flavone, and flavanone derivatives were used which were isolated compounds from *Muntingia calabura*, synthesised compounds from Institute of Science (IOS), and a library of compounds from Specs. Three known compounds namely 3,5,7-trimethoxyflavone (**MC1**), 5-hydroxy-3,7-dimethoxyflavone (**MC2**), and 5-hydroxy-7-methoxyflavone (**MC3**) were isolated from *M. calabura*. For Specs library, 767 of chalcones and 256 of flavones were filtered from a total of 460,260 compounds. These compounds were screened for drug-likeness properties using QikProp. Three isolated compounds, 40 synthesised compounds from IOS and 706 of Specs compounds passed the criteria and proceeded with docking process using GLIDE. Four subtypes of PDE involved in inflammation were chosen namely PDE4B, PDE4D, PDE3B, and PDE7D. From the docking results, two isolated compounds, six IOS compounds, and 31 Specs compounds were selective towards PDE4B and had good docking scores in PDE3B and PDE7A and continued for PDE inhibition and cytotoxicity assay. Eleven compounds were confirmed to have selectivity towards PDE4B, PDE3B and PDE7A while, nine compounds were non-toxic (IC_{50}>100) and eight compounds were moderate toxic (IC_{50}<20). Thus, the top three compounds (**MC2**, **MC3**, and **SC11**) were selected for analysis of binding interactions and MD simulation using Desmond. It was noted that the methoxyl group at 3-position played an important role in the selectivity and contributed to the stability of **MC2** in the binding pocket. All selected compounds also exhibited good ADMET profiles as predicted using multiple server-based software. But only **MC2** did not pass the blood-brain barrier which may spare it from side effects on brain. **MC2** was further investigated using inflammatory animal models. It was found that **MC2** reduced the size of paw oedema at late phase of carrageenan-induced paw oedema. **MC2** was able to inhibit granuloma formation in cotton pellet-induced granuloma. Further evaluation was done to assess the adverse effects of **MC2** on the susceptible organs. There was no notable fluctuation in liver, kidney, and cardiac enzymes as well as no histological change in organs. This project illustrated the pipeline of successful identification of lead compounds using the high throughput *in silico* computational modelling, *in vitro* cell lines and *in vivo* animal models. **MC2** was determined to have potential to become a lead compounds for multi-target subtypes PDE inhibitors.

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