Doctoral Dissertation Evaluation Review

Degree requested Doctor of Life Science Applicant's name Hadya Virupaksha Deepak

Examiner:

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Title of Doctoral Dissertation

Dual inhibitors of amyloid beta aggregation and sphingomyelin synthase from natural resources
(アミロイドβ凝集とスフィンゴミエリン合成酵素の二重阻害を示す天然資源化合物に関する研究)

Results of Evaluation of the Doctoral Dissertation (Report)

Drug design is the inventive process of finding new medications based on the knowledge of the biological target. The notion of 'one molecule – one target – one disease' has been a prevalent paradigm in pharmaceutical industry. The main idea of this approach is the identification of a single protein target whose inhibition leads to a successful treatment of the examined disease.

Modulation of the activity of a specific enzyme or receptor by a small molecule is one of the cornerstones of modern target-based drug discovery. However, small molecules frequently bind to multiple target molecules, influencing both drug efficacy and safety. Although the one-drug-hits-one target approach was dominant in the post-genomic era, it is regarded as inadequate to address complex diseases. The multitarget approach has become a fruitful area of drug discovery, particularly in developing medicines to treat major complex diseases. For example, natural products such as genistein, curcumin, and tashinone have been reported to inhibit amyloid β (Aβ) and human islet amylin (hIAPP) associated with type 2 diabetes. Another compound, miltirone, isolated from *Salvia miltiorrhiza*, was shown to be a dual inhibitor of P-glycoprotein and cell growth in doxorubicin-resistant HepG2 cells.

From author study he successfully isolated daurichromenic acid (1), as a potent dual inhibitor for sphingomyelin synthase (SMS) and amyloid beta (Aβ) aggregation inhibition. To determine the biological properties of DCA and its derivatives and whether they are promising candidate drugs, the ability of these compounds to inhibit SMS activity was analyzed, and the structure–activity relationship of these compounds were made by using cell-based SMS assays. Furthermore, the effects of DCAs and natural SMS inhibitors on Aβ aggregation were assessed by microtiter-scale high-throughput screening (MSHTS) assays. The present study showed that DCA, a terpenoid from the leaves of *Rhododendron dauricum*, is a natural inhibitor of sphingomyelin synthase. Few of its derivatives, including compounds 4, and (-) hongoquercin A, also showed good inhibitory activity against SMS. In addition, similar three compounds were found to inhibit $A\beta_{42}$ aggregation. MSHTS assays were used to evaluate amyloid beta aggregation activity using DCA and their derivatives. DCA (1) and compound 4 and (-) hongoquercin A with the presence of a carboxylic acid group

tend to inhibit both SMS and Aβ aggregation inhibition. This work was the first report on daurichromenic acid as a dual inhibitor for sphingomyelin synthase and amyloid beta aggregation.

In conclusion, the author has new findings about daurichromenic acid and its derivatives such as compound 4 and (-) hongoquercin as a dual inhibitor on sphingomyelin synthase (SMS) and amyloid beta (Aβ) aggregation which is really a great target for alzheimer's. This current study will contribute to future drug development on dual inhibition of two pathological pathways lead to one disease like alzheimer's, Parkinson's etc. Therefore, we acknowledge that the author is qualified to be granted a Doctorate of Life Science from Hokkaido University.