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Synthetic flavonoid derivatives as novel modulators of platelet function

Platelets, small circulating blood cells play indispensable roles in the regulation of haemostasis via blood clotting. However, their unwarranted activation in blood vessels leads to thrombosis, which obstructs blood flow to major organs such as heart and brain resulting in heart attack and stroke, respectively. Hence, platelets act as a promising target to treat/prevent cardiovascular diseases (primarily thrombotic diseases). Direct relationships between cardiovascular health and dietary flavonoids have been long established. Nevertheless, numerous challenges are associated with the use of dietary components in biological systems for the prevention and treatment of diseases due to their poor absorption in the intestine, the reduced bioavailability in blood stream, inability to readily cross the cell membranes and their modest stability in biological systems. Here, we report the design, synthesis, chemical characterisation and biological evaluation of Ruthenium complexes of chrysin (a natural flavonoid), and its synthesised thio-flavone and their Ruthenium derivatives for the modulation of platelet function and thrombus formation. Our results demonstrate

that Ruthenium-based synthetic chrysin derivatives exert enhanced inhibitory effects in platelets under physiological conditions. Furthermore, we explored the structure-activity relationships of flavonoids with platelets through a systematic analysis of structurally-related flavones with the view of advancing the current knowledge on structure-activity relationships of flavonoids. For this, we investigated a panel of 16 synthetic flavones containing hydroxy or methoxy groups at C-7,8 positions on the A-ring with a phenyl group or its bioisosteres as the B-ring along with their thio-analogues possessing a sulfur molecule at the 4th carbon position in the C-ring for their anti-platelet efficacies. The results demonstrate that the hydroxyl groups in flavonoids are important for optimum platelet inhibitory activities. In addition, the 4-C=O and B ring phenyl groups are less critical for the anti-platelet activity of these flavonoids. Overall, our results demonstrate that Ru-thio-chrysin could serve as a promising template for the development of novel anti-thrombotic agents and this structure-activity relationship for flavonoids on platelet function may guide the design, optimisation and development of flavonoid scaffolds as anti-platelet agents..

Biography

Sakthivel Vaiyapuri is a Lecturer in Pharmacology in the School of Pharmacy at the University of Reading, UK. He completed Bachelors in Biochemistry at Bharathidasan University and Masters in Biotechnology at the University of Madras, India. He received his PhD in the field of snake venoms and postdoctoral experience in cardiovascular diseases with specific interest on platelet signaling from the University of Reading. Currently, his research group involved in the functional characterization of inflammatory molecules such as formyl peptide and toll-like receptors in the modulation of platelet function at the interface between thrombosis and inflammation. Furthermore, his group is also engaged in analyzing the toxic components of snake venoms and their impact on various functions of cardiovascular system.

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