Preclinical Investigation to Develop Anti-Platelet and Cholesterol-Lowering Agent for Prevention and Treatment of Stroke

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Purpose of this investigation is to develop a new safe and effective therapy for stroke. Nearly a quarter of global deaths each year are caused by blood clotting. High cholesterol and platelet aggregation are the two major risk factors for stroke. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) plays a major role in platelet aggregation and atherosclerotic plaque formation. Currently there are no approved small molecule inhibitors of PCSK9. It is hypothesized that if PCSK9 plays a key role in clot formation, and increases atherosclerotic plaque vulnerability, then PCSK9 inhibitors could be developed as new agents for prevention and treatment of stroke. The crystal structure of PCSK9 enzyme was obtained from the Protein Data Bank and the five molecules with high affinity to PCSK9 were selected using molecular docking mode. The selected molecules were screened for PCSK9 inhibitory activity using ELISA method. Anti-platelet activity (preventing clotting) of PAC was tested using platelet aggregometer. Proanthocyanidin (PAC) was determined to be the best PCSK9 inhibitor. PAC concentration vs PCSK9 inhibition activity appeared to be in sigmoid shape. PAC was found to be a potent platelet inhibitor and it reduced LDL-cholesterol levels. PAC inhibited PCSK9 in a concentration range of 100 to 1000 μM. PAC demonstrated remarkable antiplatelet activity compared to the control ($p<0.001$). As PAC is not water-soluble, a nanoemulsion with globule size of around 140 nm was prepared to make it suitable for oral administration.