1. **No.**

   FP01912111

2. **Title**

   Impairment of the Neurovascular Until by the Extract of Ploom TECH, a Heat-not-burn Tobacco Product

3. **Period**

   2018-2020

4. **Summary**

Although heated tobacco products (HTPs), which allow inhalation of nicotine without burning, are expected to have less harmful chemicals induced by combustion than traditional cigarettes, it is unclear whether the use of HTPs increases the risk for cerebrovascular and neurological diseases with the blood-brain barrier (BBB) disruption. One of the HTPs distributed in Japan, Ploom TECH® was used. It heats a non-nicotine liquid, which passes through granulated tobacco leaves, to produce nicotine-containing vapor. To mimic the vapor, we extracted granulated tobacco leaves in Ploom TECH® tobacco capsule with water, glycerol or propyleneglycol at 60°C (Ploom TECH® tobacco extract; PTE). PTE mainly contains nicotine, but did not contain other compounds which are detected in the extract of traditional cigarette smoke. Using the PTE, we found that PTE induced brain endothelial barrier dysfunction through decreasing tight junction-associated proteins. This effect of PTE is independently of nicotine. Unlike cigarette smoke, PTE did not induce inflammation and oxidative stress in brain endothelial cells, suggesting that the substances extracted from HTPs is different from cigarette smoke. We also found that PTE inhibited PDGF-BB release by RBECs, suggesting that PTE attenuated the intercellular interaction between RBECs and pericytes through PDGF-BB/PDGFRβ signaling. In oligodendrocyte differentiation, PTE inhibited the maturation of OPCs to oligodendrocytes expressing myelin basic protein. PTE inhibited the nerve growth factor (NGF)-induced neurite outgrowth from PC12 cells. Thus, our results suggested that the long use of HTPs induces impairment of BBB and neuronal function leading to cerebrovascular and neurological diseases.