

Discovery of endothelial barrier protection by natural product

ABSTRACT

Vascular endothelial cells emerge as a key regulator of vascular homeostasis. Disruption of vascular endothelial barrier leads to vascular hyperpermeability which in turn contributes to a broad spectrum of the most dreadful of human diseases, including heart diseases, diabetes, atherosclerosis, and cancer. The search for permeability-modulating agent still far lacking, thus, it is a need to search for a new agent to reduce endothelial hyperpermeability. *Bixa orellana* L. has been traditionally used to treat a number of ailments, including internal inflammation. Preliminary data showed that its leaves are able to suppress inflammation induced by carrageenan. Hence, this study aimed to investigate the anti-hyperpermeability effect of *B. orellana* leaf extract (AEBO) and elucidate its mechanism of action induced by histamine. The anti-hyperpermeability activity of the extract was evaluated using histamine-induced rat paw oedema, increased peritoneal vascular permeability, nitric oxide (NO) and vascular endothelial growth factor (VEGF) measurement in animal model, while, phospholipase C (PLC) – NO – cyclic guanosine monophosphate (cGMP) signaling pathway was determined via *in vitro*. AEBO produced a significant inhibition of histamine-induced paw edema starting at 60 min time point, with maximal percentage of inhibition (60.25%) achieved with a dose of 150 mg/kg. Up to 90% of increased peritoneal vascular hyperpermeability successfully suppressed by AEBO. NO and VEGF from inflamed paw tissues was also found to be downregulated in the AEBO group. Histamine-induced increased endothelial permeability was significantly attenuated by pretreatment with AEBO in a time- and concentration-dependent manner. Moreover, AEBO also suppressed PLC, calcium, NO and cGMP signaling cascade when endothelial cells were challenged with histamine. Protein kinase C activity was also significantly abolished by AEBO under histamine condition. In conclusion, the present data suggest that AEBO could suppress histamine-induced increased vascular permeability and the activity may be closely related with the inhibition of the PLCNO-cGMP signaling and PKC activity.

Keyword: *Bixa Orellana*; Histamine; Vascular permeability