of cGMP levels using cGMP analogs will transiently increase basal permeability in both frog and rat mesentery microvessels.[26] At the same time, inhibition of the GC using LY-83583 (inhibitor of soluble GC and of cGMP production) attenuated the BK-induced increase permeability in rats.[26] Our current data again showed that the reduction of cGMP level in the BK-induced group and this indicated an elevation of cGMP level is essential to increase endothelial permeability. However, all concentrations of AEBO were capable of suppressing the production of cGMP when HUVEC was induced by BK, with 0.4 mg/mL of the extract showing the highest inhibition rate compared with the rest. All the data suggested that AEBO participates in the suppression of endothelial permeability induced by BK may via PLC-NO-cGMP signaling pathway.

Aschner *et al.*[11] observed that PKC-dependent pathway is required for increased in endothelial permeability induced by BK. On top of that, a finding from Murray *et al.*[35] also suggested that PKC may mediate increases in vascular permeability in response to BK due to the reason that sphingosine (PKC inhibitor) markedly attenuated responses to BK in an animal setting. In the present study, we observed that BK significantly upregulated PKC activity in vascular endothelial cells, but this was reduced by the pretreatment of AEBO. The reduction is significant; however, inhibition rate is <50% even in the highest concentration (0.4 mg/mL). This may be due to AEBO not being a specific target in PKC activity.

Based on the previous GC-MS analysis,[14] the major compound presented in the AEBO is acetic acid and Ruiz and Gomes[36] had documented that low concentration of acetic acid exhibited anti-histamine activity. This could be explained the anti-hyperpermeability effect of AEBO in the current study. Nonetheless, the possibility of the other compounds or minor compounds which are yet discovered in the *B. orellana* leaves exhibiting anti-inflammatory properties cannot be excluded. Current results are important and contribute toward the validation of the traditional use of this plant in the treatment of inflammatory disorders. In addition, it could be also a potential therapeutic agent to treat vascular hyper-permeability-related diseases.

CONCLUSION

The present data has shown that AEBO plays an inhibitory role in vascular inflammation, especially vascular permeability. It was clarified that AEBO suppresses BK-induced endothelial hyperpermeability via inhibiting the PLC-NO-cGMP pathway. However, the molecular mechanism including receptor identification of AEBO involved remains to be clarified and is a very attractive future target.

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Conflicts of interest

There are no conflicts of interest.

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