Identification of Zerumbone in Zingiber zerumbet Smith as a Potent Inhibitor of 12-O-Tetradecanoylphorbol-13-acetate-induced Epstein-Barr Virus Activation

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Zerumbone was isolated from the rhizomes of Zingiber zerumbet Smith as a potent inhibitor of tumor promoter 12-O-tetradecanoylphorbol-13-acetate-induced Epstein-Barr virus activation. The IC₅₀ value of zerumbone (0.14 μM) is noticeably lower than those of the anti-tumor promoters we have hitherto obtained. Interestingly, α-humulene lacking the carbonyl group at the 8-position in zerumbone was inactive (IC₅₀ > 100 μM), while 8-hydroxy-α-humulene was markedly active (IC₅₀ = 0.95 μM).

Key words: zerumbone; Epstein-Barr virus; anti-tumor promoter; chemoprevention; Zingiber zerumbet

The Epstein-Barr virus (EBV), a herpes virus lately infecting human B-lymphocytes, has been thought to be causative of some human cancers.1-5 Tumor-promoter-induced EBV activation has been used as a means of detecting anti-tumor-promoting activity.6 Tumor promoters induce EBV activation possibly through the activation of protein kinase C (PKC)7 and mitogen-activated protein kinase (MAPK).8 We have previously screened edible plants from Thailand9-10 and Indonesia9 for their inhibitory activity toward EBV activation in Raji cells, and reported their high potential for chemoprevention. In the screening tests, plant family Zingiberaceae was found to be a particularly promising source of potent anti-tumor-promoters.11-15 Since then, some of their active constituents have been isolated, e.g., 1’-acetoxychavicol acetate (Languis galanga Stuntz), cardamomin7 (Boesenbergia pandurata Holtt.) and curcumín (Zingiber cassumunar Roxb). In our continuing studies on the anti-tumor promoters from southeast Asian plants, a methanol extract from Zingiber zerumbet Smith (Zingiberaceae) was suggested to contain potently active constituents.7

Fig. 1. Structures of Zerumbone (1), α-Humulene (2), and 8-Hydroxy-α-humulene (3).

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Abbreviations: EBV, Epstein-Barr virus; NaBH₄, sodium boron hydride; TPA, 12-O-tetradecanoylphorbol-13-acetate
compounds, may provide a lead to address the mechanism of action for the tumor promoter-induced EBV activation. In conclusion, the high potential of zerumbone for chemoprevention was indicated, and its important structural element was found to be the carbonyl group at the C-8 position.

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