

Neurotrophic compounds from Indonesian *Zingiberaceae* plant, BANGLE

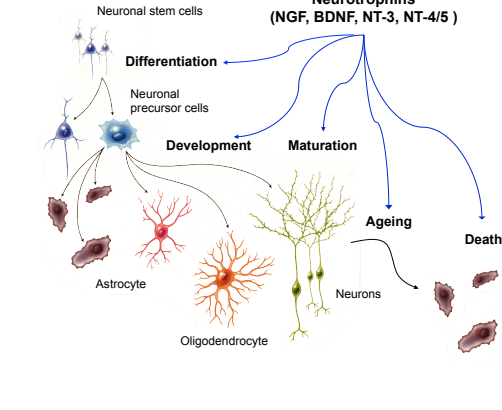
Miwa Kubo¹, Megumi Nakai², Kenichi Harada¹, Nobuaki Matsui¹, Masaaki Akagi¹, Midori Suenaga¹, Yoichi Matsunaga¹, Yoshiyasu Fukuyama¹

¹Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima, 770-8514, Japan;

²Department of Pharmacy, Kochi Medical Graduate School, Nankoku, Kochi 783-8505, Japan;

As part of our efforts to discover natural products with neurotrophic properties, we investigated the MeOH extract of the root of BANGLE (*Zingiber purpureum*) that exhibited neuritogenesis activity in PC12 cells at 25 $\mu\text{g/mL}$, resulting in the isolation of neurotrophic phenylbutenoid dimers **1** and **2**, and **3** – **5** as new compounds. Compounds **3** and **4** are the first example of curcumin coupled with phenylbutenoid. Compounds **1** and **2** found not only to significantly induce neurite sprouting of PC12 cells, but also to increase the neurite length and number of neurites in primary cultured rat cortical neurons, and also showed protective activity against cell death caused by deprivation of serum. Furthermore, chronic treatment of these compounds enhanced hippocampal neurogenesis in dementia model OBX mice. Compounds **3** and **4** had significant NGF-potentiating effects on PC12 cells. Additionally, compound **3** accelerated the prevention of A β 42 aggregation. N. Matui, Y. Kido, H. Okada, M. Kubo, M. Nakai, N. Fukuishi, Y. Fukuyama, M. Akagi, *Neuroscience Letters*, 513 (1), 72-77 (2012).

Effects of Neurotrophins



Screening of Indonesian Food Plant Extract by PC12 Cells

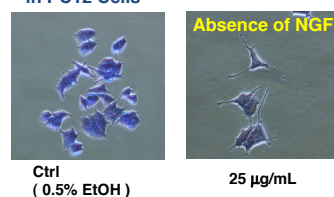
Extract	result
CABE JAWA	+
LEMPUYANG	-
DELINGO	+
BANGLE	++
MAHONI	-
TEMU HITAM	-
KUNIT MANGGA	-
GAMBIR	-
JAMBU BOL	-
JEDAM	-
SAHAMBUNTIT	+
PUKUP POLAJADI	-
CEPLE SARI	-
Mangosteen	-
Delima	+

BANGLE (*Zingiber purpureum*)

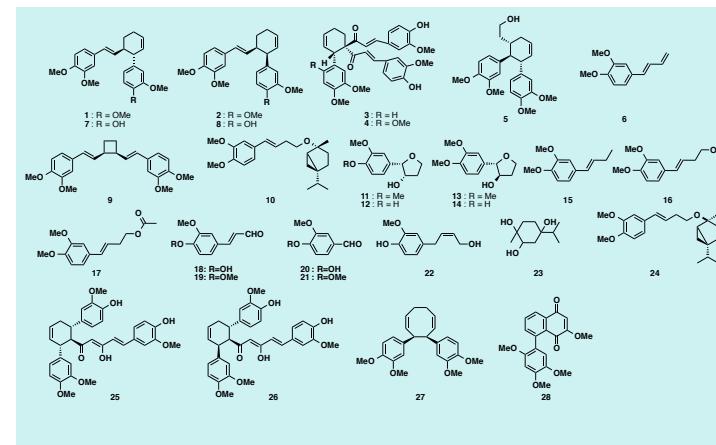


This plant is used as a spice and also used for traditional Indonesian medicine "jamu". Purpose: Fever, Headache, Stomach pain, Rheumatism, Obesity. The ingredients of herbal medicine in women after childbirth, etc...

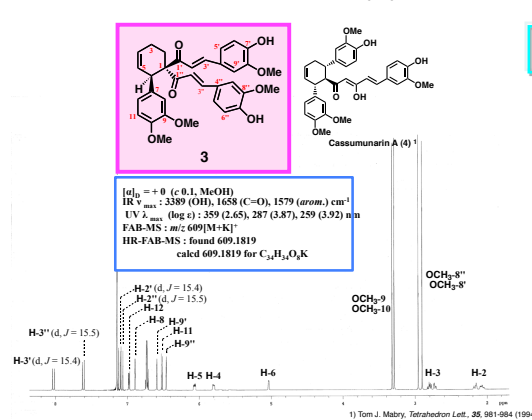
NGF-like Activity of BANGLE in PC12 Cells



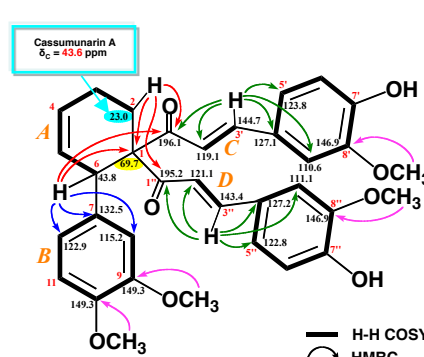
Compounds isolated from BANGLE



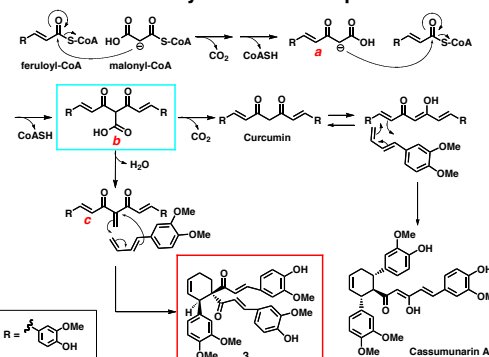
¹H NMR spectrum (600 MHz, C₆D₆) of **3**



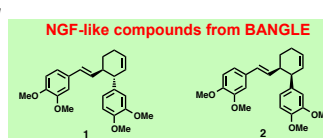
HMBC correlation of **3**



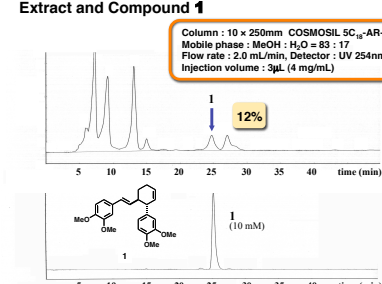
Plausible biosynthesis of compound **3**



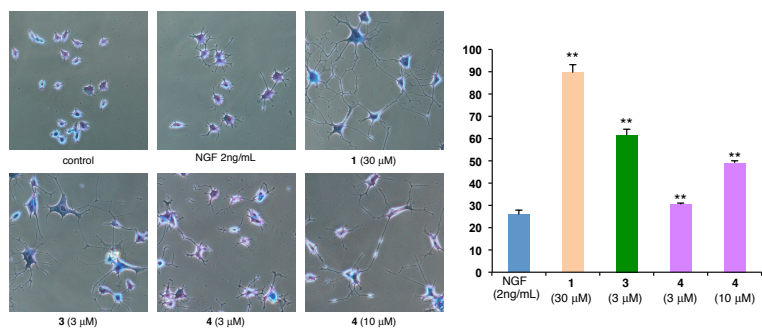
Screening



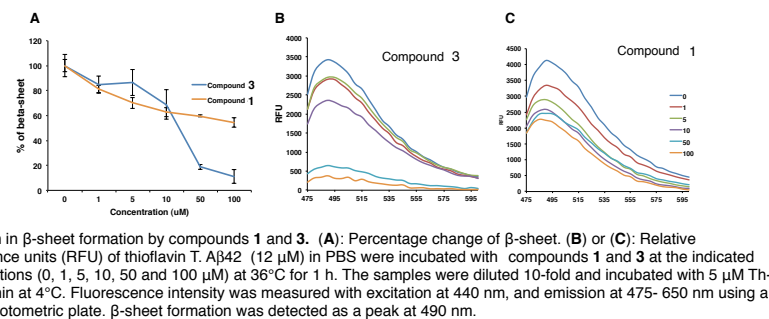
Comparison of HPLC Chromatograms between MeOH Extract and Compound **1**



Neurite Outgrowth of PC12 Cells Promoted by **3**

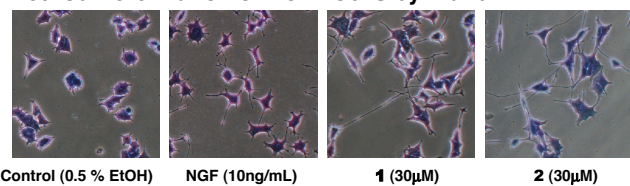


Reduction in β -sheet formation by compounds **1** and **3**.

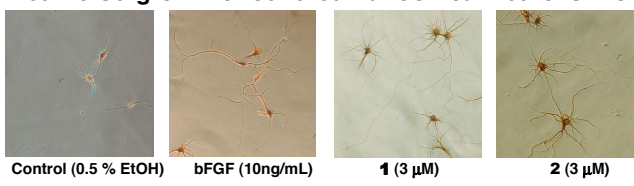


Neurotrophic Effects of **1** and **2** in Cultured Cells

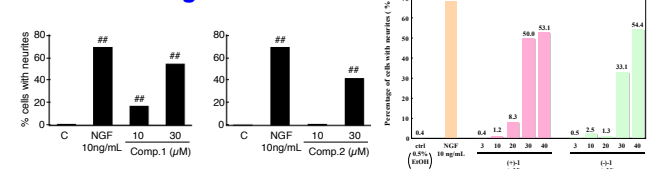
Neurodifferentiation of PC12 Cells by **1** and **2**



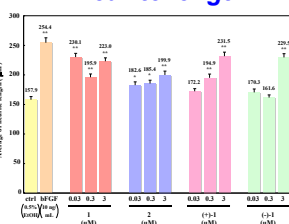
Neurite Outgrowth of Cultured Rat Cortical Neurons Promoted by **1** and **2**



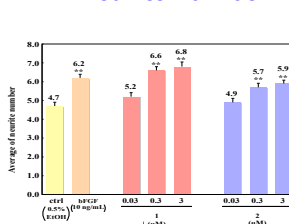
Neuritogenesis



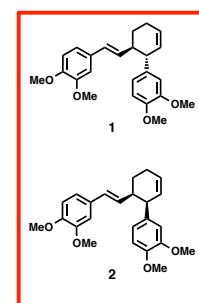
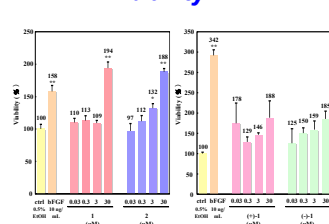
Neurite length



Neurite number

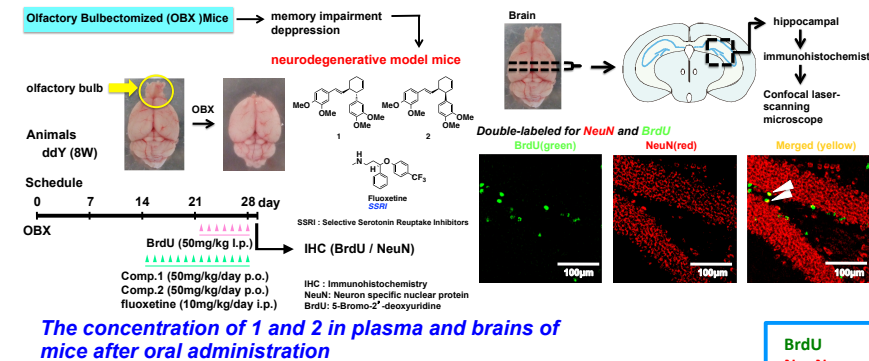


Viability

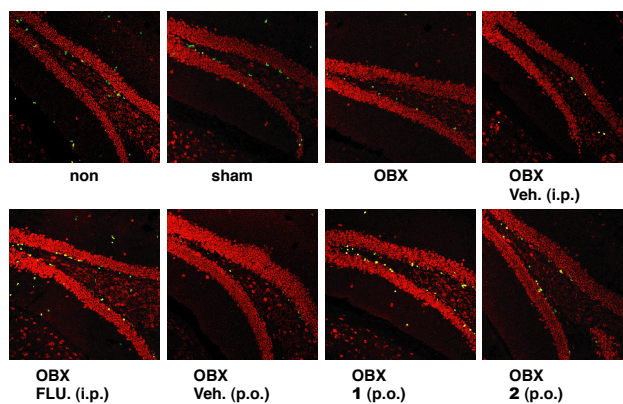


Neurogenesis Effects of **1** and **2** in OBX Mice

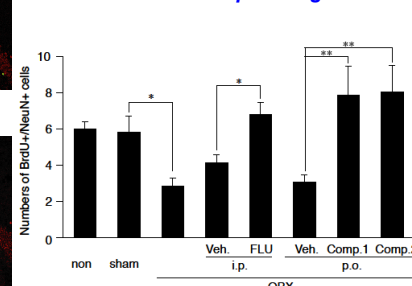
Neurogenesis of Phenylbutenoid Dimers in OBX Mice



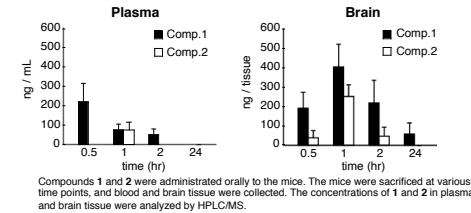
Confocal microscopy images of double staining for BrdU and NeuN in DG regions of the hippocampus.



Quantitative analysis of the number of BrdU and NeuN coexpressing cells.



The concentration of **1** and **2** in plasma and brains of mice after oral administration



Acknowledgement

We would like to thank Shinya Hosoda and Eishin Kato (Hosoda SHC Co., Ltd) for their assistance.