Chapter

Pharmacological Activities and Phytochemicals of *Etlingera pavieana* (Pierre ex Gagnep) R.M.Sm

Klaokwan Srisook and Ekaruth Srisook

Abstract

Etlingera pavieana (Pierre ex Gagnep) R.M.Sm. (Zingiberaceae family) is commonly found in Southeast Asia. The rhizome of the plant is used as a spice and folk medicine in southeastern Thailand and Cambodia. The extracts, essential oil, and compounds from *E. pavieana* were found to possess a variety of pharmacological activities like anti-inflammatory, antioxidant, antiatherogenic, and antimicrobial effects. Furthermore, phytochemical studies have reported the presence of various chemical constituents, the main being phenylpropanoids such as *trans*-4-methoxycinnamaldehyde (MCD) and 4-methoxycinnamyl *p*-coumarate (MCC). Therefore, *E. pavieana* seems to be a potential source of natural products for treatment of various diseases and promotion of good health.

Keywords: *Etlingera pavieana*, pharmacological activity, phytochemical constituents, Zingiberaceae

1. Introduction

Plant-based nutraceuticals or functional foods have gained attention due to their health promotion and safety in comparison to synthetic food ingredients [1, 2]. Presently, worldwide researchers have focus on scientific evaluation of medicinal plants to detect their pharmacological activities. Zingiberaceae family is distributed worldwide and comprises approximately 52 genera and 1587 species [3]. It is about 300 species belonging to 26 genera found in Thailand [4]. The plants in this family are the natural sources for traditional medicine, foods, spice, and other ethnobotanical uses [4]. *Etlingera pavieana* (Pierre ex Gagnep) R.M.Sm. is a member of the Zingiberaceae family and a medicinal plant of southeastern Thailand [5]. Several *in vitro* and *in vivo* pharmacological experiments and phytochemistry studies of *E. pavieana* have been reported. This chapter has presented comprehensive information about morphological characteristics, traditional uses, pharmacology activities, and phytochemical constituents of *E. pavieana*, which provide the data to plan future studies.

2. Botanical description and uses of *Etlingera pavieana* (Pierre ex Gagnep) R.M.Sm.

E. pavieana is endemic to Southeast Asia including Thailand, Cambodia, Laos, and Vietnam. This plant is locally known in Thai as rew-hom/raew hawm [5]. It is a perennial rhizomatous herb. The leafy shoots can grow to a height of 1–2.5 m (**Figure 1A**). The leaves are narrowly obovate, green, and glabrous (**Figure 1B**). The rhizomes are long-creeping, slender (0.7–1.5 cm in diameter), and fragrant (**Figure 1C**). Inflorescence arises from the rhizomes and is partially embedded in the ground (**Figure 1D**). To date *E. pavieana* is found in the natural habitats and cultivated in fruit gardens in southeastern Thailand for commercial purposes as food and herbs [5]. The young shoots are eaten as a culinary vegetable, and the rhizomes are used as a spice, an ingredient in noodle soup "Moo Lieng," and as medicines. The reported medicinal uses of the rhizomes are relieving fever and flatulence and helping the digestive system and diuresis [5, 6]. In Cambodia, the *E. pavieana* rhizome is boiled in water with *Amomum verum* Blackw. and sugar to make a drink as a tonic and as a medicine for relieving stomach disorder and pharyngitis [5].

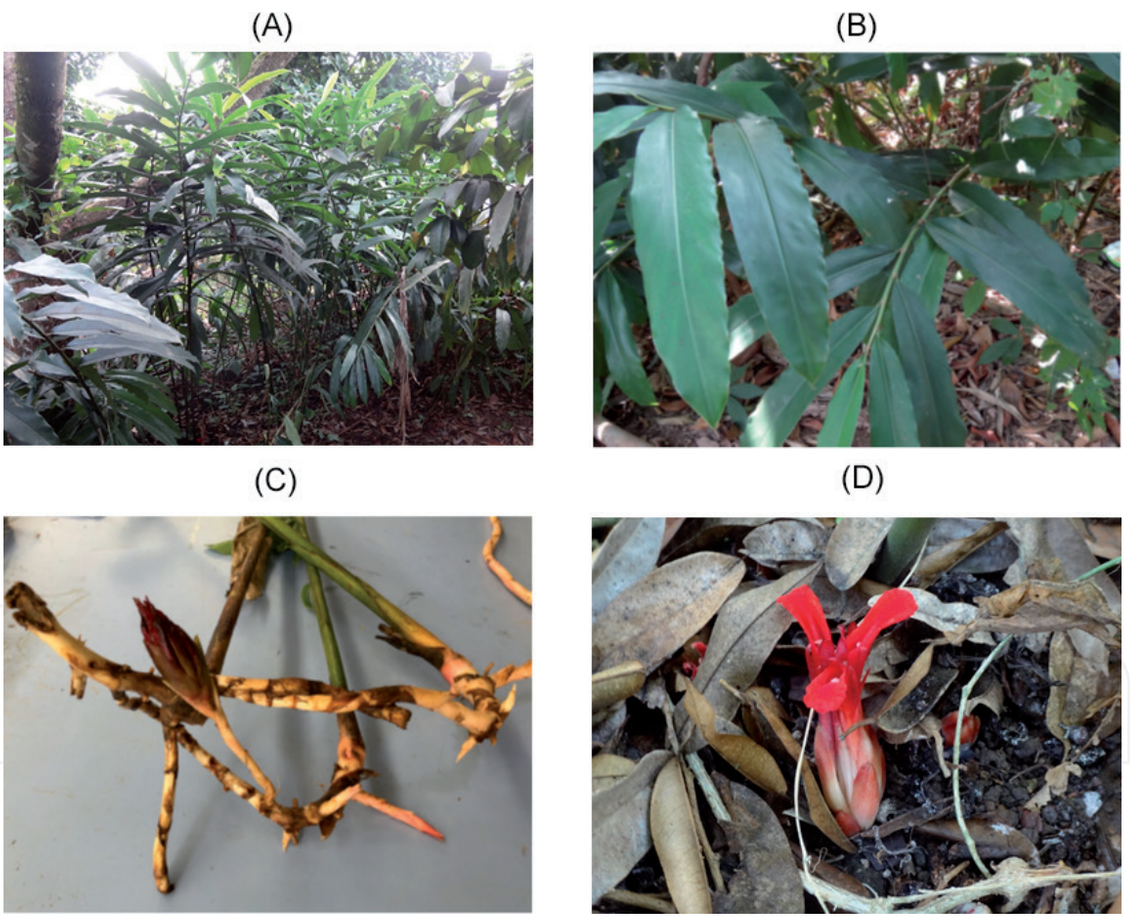

Figure 1.
Etlingera pavieana (Pierre ex Gagnep) R.M.Sm. whole plant (A), leaves (B), rhizomes (C), inflorescence (D) (Photographed by Srisook, K).

3. Phytochemical constituents of *E. pavieana*

It has been recently reported that the investigation of rhizomes of *Etlingera pavieana* from Thailand resulted in isolation of an uncommon compound which is (E)-((E)-3-(4-methoxyphenyl)ally) 3-(4-hydroxyphenyl) acrylate or 4-methoxycinnamyl *p*-coumarate (MCC) (**1**) and a series of phenylpropanoids such as

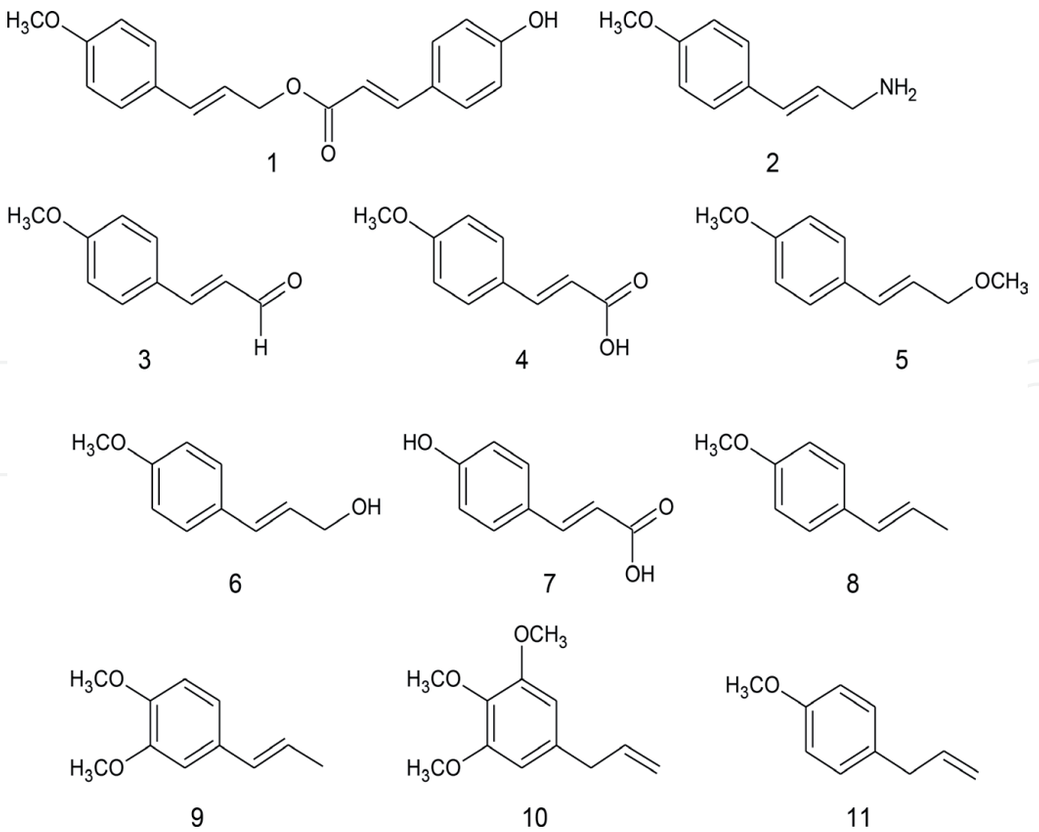

Figure 2.
Chemical structures of some phytochemicals from rhizomes and leaves of E. pavieana.

(E)-3-(4-methoxyphenyl)prop-en-1-amine (**2**), 3-(4-methoxyphenyl) prop-2-enal, or *trans*-4-methoxycinnamaldehyde (MCD) (**3**), (E)-4-methoxycinnamic acid (**4**), and (E)-1-methoxy-4-(3-methoxyprop-1-enyl) benzene (**5**) as shown in **Figure 2** [7]. Moreover, Srisook et al. have reported the isolation of the bioactive compound **1** and its two precursors, (2E)-3-(4-methoxyphenyl)prop-2-en-1-ol or 4-methoxycinnamyl alcohol (MCA) (**6**) and (E)-3-(4-hydroxyphenyl)prop-2-enoic acid or *p*-coumaric acid (CM) (**7**), from the rhizome of *E. pavieana* by activity-guided isolation [8]. The other three common phenylpropanoids, (E)-4-methoxycinnamaldehyde (**3**), *trans*-anethole (**8**), and *trans*-methyl isoeugenol (**9**), were also extracted from the plant by Srisook and colleagues (unpublished data).

The essential oil investigation of rhizome of *E. pavieana* resulted in *trans*-anethole (**8**) (48.5%) and elemicin (**10**, 13.8%) as major compounds [9], while Srisook et al. have investigated that the hydrodistillation of leaves of *E. pavieana* yielded methyl chavicol (**11**) as the most predominant product (93%) (unpublished data).

4. Pharmacological activities of *E. pavieana*

It is reported that *E. pavieana* possess various pharmacological activities such as antioxidant [10, 11]; antimicrobial [7, 12]; anticancer against breast, cervix, liver, colon, and small cell lung cancer [7, 13]; and anti-inflammatory effects[8, 14–16]. The detailed information is shown below.

4.1 Anti-inflammatory effect

Inflammation is a complex biological response to pathogenic agents and chemical as well as physical stimuli to get rid of the stimulants [17]. Macrophages are inflammatory cells that are considered as the first line of defense against various

stimuli [18]. Upon contact with injurious stimuli, macrophages are activated and produce a large amount of inflammatory mediators and cytokines such as reactive oxygen species (ROS), nitric oxide (NO), prostaglandins (PGs), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and IL-12 [19–24]. It is well-known that excess and prolonged secretion of these mediators and cytokines has participated in the pathogenesis of a variety of inflammatory diseases such as inflammatory bowel diseases [25], osteoarthritis [26], cancer [23], multiple sclerosis [27], neurodegenerative diseases like Alzheimer's disease and Parkinson's disease [28–30], atherosclerosis, and cardiovascular diseases [24, 31–33]. Therefore, substances inhibiting the secretions of these mediators and cytokines may be used to treat or prevent a variety of inflammation-related diseases. Since some Zingiberaceae species including *Curcuma comosa* [34], *Amomum tsao-ko* [35], *Kaempferia parviflor*a [36], *Zingiber officinale* [37], *Alpinia officinarum* [38], *Alpinia pricei* Hayata [39], and *Alpinia katsumadai* Hayata [40] exhibit anti-inflammatory effects *in vitro* and *in vivo*, Srisook and colleagues, therefore, designed the experiment to determine anti-inflammatory activity of *E. pavieana* using lipopolysaccharide (LPS)- induced inflammation in RAW 264.7 murine macrophage cell model. A 95% ethanol extract of *E. pavieana* rhizomes was successively fractionated with hexane and ethyl acetate which was evaluated for anti-inflammatory effect on macrophage cells by inhibiting the production of inducible nitric oxide synthase (iNOS)-catalyzed NO. The hexane, ethyl acetate, and water fractions of rhizomal ethanol extracts of *E. pavieana* displayed anti-inflammatory effect on macrophage cells. Among them, ethyl acetate fraction was the most potent fraction. Furthermore, activity-guided isolation of this fraction showed that the bioactive compounds were phenolic compounds including 4-methoxycinnamyl alcohol (MCA), *trans*-4-methoxycinnamaldehyde (MCD), 4-methoxycinnamyl *p*-coumarate (MCC), and p-coumaric acid (CM) [8].

Mankhong et al. reported that 4-methoxycinnamyl *p*-coumarate, as the most potent compound extracted from *E. pavieana* rhizomes, exhibited an inhibitory effect on the production of cyclooxygenase-2 (COX-2)-catalyzed PGE_2, NO, IL-1β, and TNF-α on LPS-stimulated RAW 264.7 murine macrophages with IC_{50} values of 14.1 ± 2.3, 32.7 ± 4.7, 3.0 ± 0.5, and 26.8 ± 5.7 μM, respectively. MCC compound inhibited gene expression of iNOS, COX-2, IL-1β, and TNF-α in a concentration-dependent manner through downregulating NF-κB, PI3K/Akt, and AP-1 signaling pathways [14, 16]. Furthermore, MCC attenuated LPS-reduced COX-1 expression in LPS-stimulated RAW 264.7 macrophages. It suggests that MCC possesses anti-inflammatory activity with selective inhibitory effect on COX expression [14].

Recently, *trans*-4-methoxycinnamaldehyde, another compound isolated from *E. pavieana* rhizomes, suppressed the formation of NO and PGE_2 as well as the expression of their synthesizing enzymes, iNOS and COX-2, on LPS- and Pam3CSK4-induced RAW 264.7 cells. The IC_{50} values of NO and PGE_2 inhibition were 49.9 ± 4.7 and 87.6 ± 5.6 μM, respectively. The mechanism underlying anti-inflammatory activity of MCD could be inactivation of NF-κB and JNK/c-Jun signaling pathways [15]. Moreover, MCD showed a significant anti-inflammatory activity in rat models of acute inflammation. It was evident from this study that MCD (3 mg/ear) reduced ethyl phenylpropiolate (EPP)-induced ear edema by 51.5% inhibition. The second animal model used in this study was carrageenan-induced paw edema. Rats were orally administrated with MCD at doses of 75, 150, and 300 mg/kg for 1 h before injection with carrageenan. MCD can significantly decrease paw edema in a dose-dependent manner at 1, 3, and 5 h after carrageenan stimulation. Since edema formation induced by EPP and carrageenan is attributed to a release of several inflammatory mediators [41, 42], it is implied that the mode of MCD anti-inflammatory action *in vivo* model is mediated in part by suppression of inflammatory mediators.

We also investigated anti-inflammatory effect of essential oil of *E. pavieana* leaves on LPS-induced RAW 264.7 macrophages. The essential oil of *E. pavieana* leaves at 25–100 μg/mL exhibited a concentration-dependent inhibition effect on NO production without significant cytotoxicity (**Figure 3A**). Incubation of cells with essential oil caused reduction of iNOS protein and mRNA expression (**Figure 3B, C**). The compound responsible for anti-inflammatory effect of essential oil of *E. pavieana* leaves might be methyl chavicol, a main phytoconstituent of this essential oil (unpublished data).

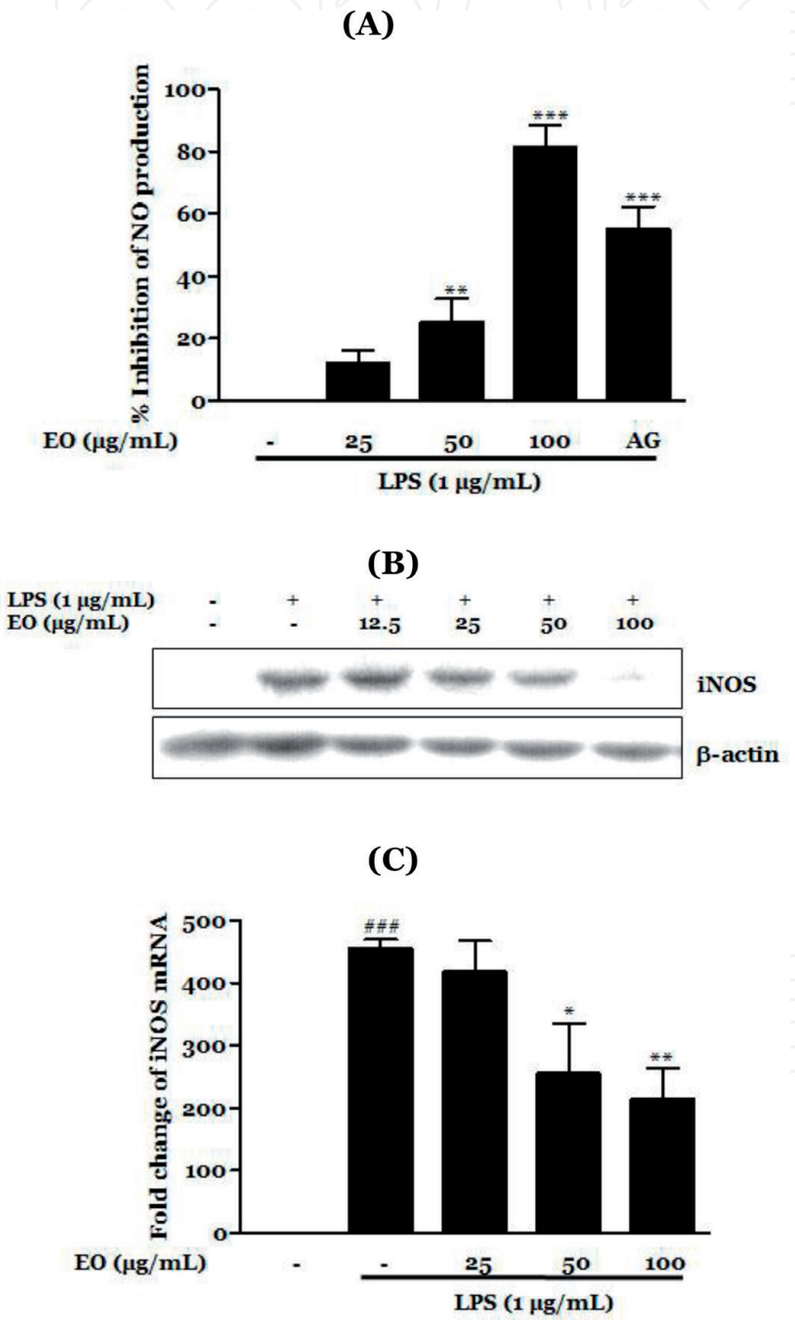

Figure 3.
The inhibitory effect of essential oil of E. pavieana leaves (EO) on LPS-induced NO production (A) and iNOS expression. RAW 264.7 cells were incubated with essential oil of E. pavieana leaves and LPS for 24 h for determination of NO production and iNOS protein as well as 9 h for mRNA expression. Supernatant was collected for the analysis of NO production by Griess reaction. Cells were lysed and determined for protein (B) and mRNA (C) expression by Western blot analysis and real-time RT-PCR, respectively. $^{###}p < 0.001$ *compared to unstimulated control cells,* $^{*}p < 0.05$, $^{**}p < 0.01$, *and* $^{***}p < 0.001$, *was significantly different from LPS-stimulated cells. AG = cells treated with 50 μM aminoguanidine, an iNOS inhibitor.*

4.2 Antiatherogenic effect

Atherosclerosis is a chronic inflammatory disorder which leads to cardiovascular diseases (CVDs) [43, 44]; it is a major cause of death in the world [24, 45]. Endothelial dysfunction is an early step in the development of atherosclerosis. It involves with reduced NO bioavailability, low-grade inflammation, and oxidative stress [44, 46–48]. The initiation of atherosclerotic lesion is influenced by the expression of cell adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) on the vascular surface of the endothelial cells resulting in recruitment of leukocytes into the vascular tissue [49]. Inhibiting the expression of ICAM-1 and VCAM-1 leads to reduction of leukocyte emigration and retardation of the development of atherosclerosis. Thus, the substance that inhibits the expression of these cell adhesion molecules may be considered as anti-atherosclerosis agent that prevents vascular inflammatory disorders.

The rhizomal ethanol extract of *E. pavieana* was assessed for its anti-vascular inflammatory effect in human umbilical vein endothelial cells (EA.hy926 cells). Endothelial activation is upregulated by various pro-inflammatory cytokines, including TNF-α secreted under inflammatory conditions. The *E. pavieana* extract inhibited TNF-α-induced expression of ICAM-1 and VCAM-1 protein and mRNA in a concentration-dependent manner. The inhibitory effect of the rhizome extract in endothelial cells is caused from interfering with the activation of NF-κB and JNK/c-Jun signaling pathways. Moreover, Akt activation by *E. pavieana* rhizome is associated with negative regulation of inflammation. This anti-vascular inflammatory activity was attributed in part due to the presence of the two most active phenolic compounds of which were 4-methoxycinnamyl *p*-coumarate and *trans*-4-methoxycinnamaldehyde [50].

It is believed that decrease in endothelium-derived NO, produced by endothelial NO synthase (eNOS), results in reduced NO bioavailability [44, 49]. Another study was carried out to demonstrate antiatherogenic effect of *E. pavieana* rhizome. EA.hy926 endothelial cells incubated with the ethanol extract of *E. pavieana* rhizome (12.5–200 μg/mL) caused increased NO level in a concentration-dependent manner. This induction might be partly mediated by the activation of eNOS enzyme via phosphorylation at Ser1177 [11].

4.3 Antioxidant effect

Accumulating evidences suggest that not only inactivation of eNOS enzyme but also increased superoxide level leads to the reduction in NO bioavailability [24, 49]. Superoxide anion is produced by the mitochondrial electron transport chain and several enzymes in the endothelial cells. Superoxide anion is then oxidized to hydrogen peroxide and other physiological reactive species such as hydroxyl radical and hypochlorous acid [44]. Moreover, it reacts with NO to form highly reactive peroxynitrite leading to eNOS dysfunction [24, 47]. Chronic inflammation is also closely associated with oxidative stress which generated excess ROS [24].

The hexane, ethyl acetate, and water fractions of ethanol extract of *E. pavieana* rhizomes have shown *in vitro* antioxidant effects, which are evaluated by various antioxidant activity assays including 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, reducing power and ferrous ion chelating activity [10]. *E. pavieana* rhizomal extract has also been assayed, its ROS scavenging activity in EA.hy926 endothelial cells, using 2,7-dichlorodihydrofluorescein diacetate (H_2DCF-DA) probe. TNF-α markedly induced ROS formation, while the extract (25–100 μg/mL) concentration dependently inhibited ROS level [11]. Thus, the data indicate antioxidant effect of *E. pavieana* mediated in part by counteract with ROS.

4.4 Anticancer activity

A number of plant-derived compounds can prevent progression of cancer [51, 52] and possess anticancer activity [53]. The ethanol extract from *E. pavieana* rhizomes exhibits cytotoxic effect against several cancer cell lines such as breast adenocarcinoma MDA-MB-231, hepatoma $HepG_2$, cervical carcinoma HeLa, and C33A. The IC_{50} values were ranging from 160 to 192 μg/mL, respectively. Trans-4-methoxycinnamaldehyde, an active compound isolated by cytotoxicity-guided isolation from *E. pavieana* rhizomes, has shown cytotoxic effects against C33A, colorectal carcinoma HCT116, MDA-MB-231, and $HepG_2$ with the IC_{50} values of 34.3, 38.7, 39.3, and 40.7 μM, respectively [13]. Tachai and Nuntawong [7] reported that 4-methoxycinnamyl *p*-coumarate exhibited inhibitory activity on cell growth of human breast cancer (MCF7), human oral cavity cancer (KB), and human small cell lung cancer (NCI-H187) with IC_{50} values of 25.1, 20.2, and 34.8 μM, respectively [7]. Essential oil from the rhizomes was found to have cytotoxic effect against NCI-H187 (IC_{50}: 31.7 μg/mL) [7].

4.5 Antimicrobial activity

Various solvent extracts of *E. pavieana* (ethanol, acetone, dichloromethane, ethyl acetate, petroleum ether, and hexane) were found to be active against Gram-positive bacteria *(Bacillus cereus*, *B. subtilis*, *Staphylococcus aureus*, *Listeria monocytogenes*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Vibrio parahaemolyticus*, and *Salmonella typhimurium*). Antimicrobial activity of leaves was higher than that of stem and rhizome [12]. Tachai and Nuntawong demonstrated that hexane, dichloromethane, and methanol extracts of *E. pavieana* rhizomes were inactive against *Mycobacterium tuberculosis*, while MCC exhibited its antimicrobial activity against *M. tuberculosis* with minimum inhibitory concentration at 50 μg/mL [7].

5. Conclusion

In this chapter, we have provided the information on botanical aspects, dietary and traditional uses, phytochemicals, and pharmacological activities of *Etlingera pavieana* which is distributed in Southeast Asia. The major active compounds are phenylpropanoids such as *trans*-4-methoxycinnamaldehyde, and 4-methoxycinnamyl *p*-coumarate. Its rhizomes exhibit anti-inflammatory, antioxidant, antiatherogenic, antimicrobial, and anticancer activities. The pharmacological activities reported here confirm therapeutic efficacy of *E. pavieana* rhizomes which might be developed into medicines or nutraceuticals for the treatment and prevention of various diseases, especially inflammation-related diseases. However, in vivo toxicology studies of *E. pavieana* rhizomes should be performed along with the clinical trials.

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Conflict of interest

The authors have no conflict of interest to declare.

Author details

Klaokwan Srisook[1,2*] and Ekaruth Srisook[2,3]

1 Faculty of Science, Department of Biochemistry and Research Unit of Natural Bioactive Compounds for Healthcare Products Development, Burapha University, Chonburi, Thailand

2 Faculty of Science, Center of Excellence for Innovation in Chemistry, Burapha University, Chonburi, Thailand

3 Faculty of Science, Department of Chemistry and Research Unit of Natural Bioactive Compounds for Healthcare Products Development, Burapha University, Chonburi, Thailand

*Address all correspondence to: klaokwan@buu.ac.th

References

[1] Pandey N, Meena RP, Rai SK, Pansey-Rai S. Medicinal plants derived nutraceuticals: A Re-emerging health aid. International Journal of Pharma and Bio Sciences. 2011;**2**(4):420-441

[2] Srivastava RK. Need of nutraceuticals/functional food products for health benefits to world-wide people. Journal of Biotechnology and Biomedical Science. 2018;**1**(4):1-13. DOI: 10.14302/issn.2576-6694.jbbs-18-2408

[3] The Plant List. Version 1.1 [Internet]. 2013. Available from: http://www.theplantlist.org/ (accessed 1st January). [Accessed: 24-07-2019]

[4] Larsen K, Larsen SS. Gingers of Thailand. Chiang Mai, Thailand: Queen Sirikit Botanic Garden; 2006. 184p

[5] Poulsen DA, Phonsena P. Morphological variation and distribution of the useful ginger *Etlingera pavieana* (Zingiberaceae). Nordic Journal of Botany. 2017;**35**:467-475

[6] Phonsena P. Medicinal Plants in Khao Hin Son Herb Garden. Prachinburi: Jettanaromphun Printing; 2007. 301 p. (In Thai)

[7] Tachai S, Nuntawong N. Uncommon secondary metabolites from *Etlingera pavieana* rhizomes. Natural Product Research. 2016;**30**:2215-2219

[8] Srisook E, Palachot M, Mankhong S, Srisook K. Anti-inflammatory effect of *Etlingera pavieana* (Pierre ex Gagnep.) R.M.Sm. rhizomal extract and its phenolic compounds in lipopolysaccharide-stimulated macrophages. Pharmacognosy Magazine. 2017;**13**:s230-s235

[9] Tachai S, Wangkarn S, Nuntawong N. Chemical constituents of the rhizome oils of *Etlingera pavieana* (Pierre ex Gagnep.) R.M.Sm. Biochemical Systematics and Ecology. 2014;**57**:410-415

[10] Srisook K, Srisook E. Evaluation of antioxidant capacity of fractions from *Etlingera pavieana* (Pierre ex Gagnep.) R.M.Sm. rhizome. In: Proceedings of the 3rd International Natural Products for Health and Beauty; 16-18 March 2011; Thailand: Chiang Mai University

[11] Srisook K, Udompong S, Sawai P, Thongyen T. *Etlingera pavieana* rhizome extract decreases oxidative stress and activates eNOS activity via stimulation of Akt phosphorylation in human endothelial cells. Naresuan Phayao Journal. 2018;**11**:23-28

[12] Naksang P, Rachtanapun C. Effect of sample preparation on antibacterial activity of *Etlingera pavieana* (Pierre ex Gagnep.) R.M.Sm. extracts against foodborne bacteria. In: Proceedings of the 53rd Kasetsart University Annual Conference: Innovation for Bio-Health Supplements; February 2015; Thailand: Kasetsart University

[13] Iawsipo P, Srisook E, Ponglikitmongkol M, Tatiyar S, Singaed O. Cytotoxic effects of *Etlingera pavieana* rhizome on various cancer cells and identification of a potential anti-tumor component. Journal of Food Biochemistry. 2018;**42**:e12540:1-9

[14] Mankhong S, Srisook E, Srisook K. Anti-inflammatory activity of 4-methoxycinnamyl *p*-coumarate isolated from *Etlingera pavieana* rhizomes in lipopolysaccharide-induced macrophages. NU International Journal of Science. 2017;**14**:58-66

[15] Srisook K, Mankhong S, Chiranthanut N, Kongsamak K, Kitwiwat N, Tongjurai P, et al.

Anti-inflammatory effect of *trans*-4-methoxycinnamaldehyde from *Etlingera pavieana* in LPS-stimulated macrophages mediated through inactivation of NF-κB and JNK/c-Jun signaling pathways and in rat models of acute inflammation. Toxicology and Applied Pharmacology. 2019a;**371**:3-11

[16] Mankhong S, Iawsipo P, Srisook E, Srisook K. 4-methoxycinnamyl *p*-coumarate isolated from *Etlingera pavieana* rhizomes inhibits inflammatory response via suppression of NF-kB, Akt and AP-1 signaling in LPS-stimulated RAW 264.7 macrophages. Phytomedicine. 2019;**54**:89-97

[17] Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 9th ed. Philadelphia, PA: Elsevier/Saunders; 2013. 928 p

[18] Kumar V. Macrophages: The potent immunoregulatory innate immune cells. In: Bhat KH, editor. Macrophage at the Crossroads of Innate and Adaptive Immunity. London: IntechOpen; 2019

[19] MacMicking J, Xie QW, Nathan C. Nitric oxide and macrophage function. Annual Review of Immunology. 1997;**15**:323-350

[20] Sherwood ER, Toliver-Kinsky T. Mechanisms of the inflammatory response. Best Practice and Research. Clinical Anaesthesiology. 2004;**18**:385-405

[21] FujiwaraN, KobayashiK. Macrophages in inflammation. Current Drug Targets. Inflammation and Allergy. 2005;**4**:281-286

[22] Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. Wound Repair and Regeneration. 2008;**16**(5):585-601

[23] Fernandes JV, Cobucci RNO, Jatobá CAN, Fernandes TA, de Azevedo JWV, de Araújo JMG. The role of the mediators of inflammation in cancer development. Pathology and Oncology Research. 2015;**21**(3):527-534. DOI: 10.1007/s12253-015-9913-z

[24] Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vascular Pharmacology. 2018;**100**:1-19

[25] Soufli I, Toumi R, Rafa H, Touil-Boukoffa C. Overview of cytokines and nitric oxide involvement in immuno-pathogenesis of inflammatory bowel diseases. World Journal of Gastrointestinal Pharmacology and Therapeutics. 2016;7(3):353-360. DOI: 10.4292/wjgpt.v7.i3.353

[26] Philp AM, Davis ET, Jones SW. Developing anti-inflammatory therapeutics for patients with osteoarthritis. Rheumatology. 2017;**56**(6):869-881. DOI: 10.1093/rheumatology/kew278

[27] Grigoriadis N, van Pesch V. A basic overview of multiple sclerosis immunopathology. European Journal of Neurology. 2015;**22**(Suppl. 2):3-13. DOI: 10.1111/ene.12798

[28] Lull ME, Block ML. Microglial activation and chronic neurodegeneration. Neurotherapeutics. 2010;7(4):354-365

[29] Koppula S, Kumar H, Kim IS. Reactive oxygen species and inhibitors of inflammatory enzymes, NADPH oxidase, and iNOS in experimental models of Parkinson's disease. Mediators of Inflammation. 2012;**2012**:16-16

[30] Asiimwe N, Yeo SG, Kim MS, Jung J, Jeong NY. Nitric oxide: Exploring the contextual link with Alzheimer's disease. Oxidative and Cellular

Longevity. 2016. Article ID 7205747, 10 pages. DOI: 10.1155/2016/7205747

[31] Khan R, Spagnoli V, Tardif JC, Allier P. Novel anti-inflammatory therapies for the treatment of atherosclerosis. Atherosclerosis. 2015;**240**:497-509

[32] Shayganni E, Bahmani M, Asgary S, Rafieian-Kopaei M. Inflammaging and cardiovascular disease: Management by medicinal plants. Phytomedicine. 2016;**23**:1119-1126

[33] Welsh P, Grassia G, Botha S, Sattar N, Maffia P. Targeting inflammation to reduce cardiovascular disease risk: A realistic clinical prospect? British Journal of Pharmacology. 2017;**174**:3898-3913

[34] Jantaratnotai N, Utaisincharoen P, Piyachaturawat P, Chongthammakun S, Sanvarinda Y. Inhibitory effect of *Curcuma comosa* on NO production and cytokine expression in LPS-activated microglia. Life Sciences. 2006;**78**:571-577

[35] Lee KY, Kim SH, Sung SH, Kim YC. Inhibitory constituents of lipopolysaccharide-induced nitric oxide production in BV2 microglia isolated from *Amomum tsao-ko*. Planta Medica. 2008;**74**:867-886

[36] Sae-Wong C, Tansakul P, Tewtrakul S. Anti-inflammatory mechanism of *Kaempferia parviflora* in murine macrophage cells (RAW264.7) and in experimental animals. Journal of Ethnopharmacology. 2009;**124**:576-580

[37] Jung HW, Yoon CH, Park KM, Han HS, Park YK. Hexane fraction of *Zingiberis rhizoma* crude extract inhibits the production of nitric oxide and pro-inflammatory cytokines in LPS-stimulated BV2 microglial cells via the NF-kappa B pathway. Food and Chemical Toxicology. 2009;**47**:1190-1197

[38] Lee JS, Kim KA, Jeong SH, Lee SG, Park HJ, Kim NJ, et al. Anti-inflammatory, anti-nociceptive, and anti-psychiatric effects by the rhizomes of *Alpinia officinarum* on complete Freund's adjuvant-induced arthritis in rats. Journal of Ethnopharmacology. 2009;**126**:258-264

[39] Yu YS, Hsu CL, Yen GC. Anti-inflammatory effects of the roots of *Alpinia pricei* Hayata and its phenolic compounds. Journal of Agriculture and Food Chemistry. 2009;**57**:7673-7680

[40] Lee MY, Seo CS, Lee JA, Shin IS, Kim SJ, Ha HK, et al. *Alpinia katsumadai* HAYATA seed extract inhibit LPS-induced inflammation by induction of heme oxygenase-1 in RAW264.7 cells. Journal of Inflammation. 2011;**10**:1007-1019

[41] Carlson R, O'Neill-Davis L, Chang J, Lewis A. Modulation of mouse ear edema by cyclooxygenase and lipoxygenase inhibitors and other pharmacologic agents. Agents and Actions. 1985;**17**:197-204

[42] Mansouri MT, Hemmati AA, Naghizadeh B, Mard SA, Rezaie A, Ghorbanzadeh B. A study of the mechanisms underlying the anti-inflammatory effect of ellagic acid in carrageenan-induced paw edema in rats. Indian Journal of Pharmacology. 2015;**47**:292-298

[43] Stoner L, Lucero A, Palmer BR, Jones LM, Young JM, Faulkner J. Inflammatory biomarkers for predicting cardiovascular disease. Clinical Biochemistry. 2013;**46**:1353-1371

[44] Haybar H, Shahrabi S, Rezaeeyan H, Shirzad R, Saki N. Endothelial cells: From dysfunction mechanism to pharmacological effect in cardiovascular disease. Cardiovascular Toxicology 2019;**19**:13-22

[45] World Health Organization. Global Status Report on Noncommunicable Diseases 2014 [Internet]. 2014. Available from: https://www.who.int/nmh/publications/ncd-status-report-2014/en/ [Accessed: 2 July, 2019]

[46] Clapp BR, Hingorani AD, Kharbanda RK, Mohamed-Ali V, Stephens JW, Vallance P, et al. Inflammation-induced endothelial dysfunction involves reduced nitric oxide bioavailability and increased oxidant stress. Cardiovascular Research. 2004;**64**(1):172-178

[47] Vanhoutte PM, Shimokawa H, Tang EH, Feletou M. Endothelial dysfunction and vascular disease. Acta Physiologica (Oxford). 2009;**196**:193-222

[48] Park KH, Park WJ. Endothelial dysfunction: Clinical implications in cardiovascular disease and therapeutic approaches. Journal of Korean Medical Science. 2015;**30**(9):1213-1225

[49] Čejková S, Králová-Lesná I, Poledne R. Monocyte adhesion to the endothelium is an initial stage of atherosclerosis development. Cor et Vasa. 2016;**58**(4):e419-e425

[50] Srisook K, Potiprasart K, Sarapusit S, Park CS, Srisook E. *Etlingera pavieana* extract attenuates TNF-α induced vascular adhesion molecule expression in human endothelial cells through NF-κB and Akt/JNK pathways. Inflammopharmacology. 2019b submitted

[51] Butt MS, Naz A, Sultan MT, Qayyum MMN. Anti-oncogenic perspectives of spices/herbs: A comprehensive review. EXCLI Journal. 2013;**12**:1043-1065

[52] Madigan M, Karhu E. The role of plant-based nutrition in cancer prevention. Journal of Unexplored Medical Data. 2018;**3**:9. DOI: 10.20517/2572-8180.2018.05

[53] Roy A, Ahuja S, Bharadvaja N. A review on medicinal plants against cancer. Journal of Plant Sciences and Agricultural Research. 2017;**2**(1:008):1-5