

19th Annual

MEDICINAL & PHARMACEUTICAL SCIENCES CONGRESS

March 25-26, 2019 Hong kong

Anti-cancer activity of (-)-kusunokinin from Piper nigrum L. in cancer cell lines and NMU-induced mammary tumorigenesis rats**Aman Tedasen, Sirinapa Dokduang, Yaowapa Sukpondma, Varomyalin Tipmanee, Narissara Lailerd and Potchanapond Graidist**
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Introduction & Objective: (-)-Kusunokinin, a lignan compound, which extracted from Piper nigrum, showed similar chemical structure with etoposide, a chemotherapeutic drug. This compound has a potent cytotoxic effect on breast cancer cell lines through the inhibition of cell cycle progression at G2/M phase, reduction of topoisomerase II and bcl-2 and promotion of p53, p21, bax, cytochrome c, caspase-8, caspase-7 and caspase-3. This current study aims to isolate (-)-kusunokinin from a large scale (22 kg) of black pepper seeds, identify (-)-kusunokinin targeted protein and investigate the anti-cancer activity in mammary tumorigenesis rats.

Method: Firstly, breast (MCF-7, MDA-MB-468 and MDA-MB-231), colon (SW-620 and HT-29) and lung (A-549) cancer cell lines were treated with (-)-kusunokinin to determine the cytotoxic activity using MTT assay.

Result: The result showed that (-)-kusunokinin strongly inhibited MCF-7 and HT-29 cells with IC₅₀ values of 3.08±0.39 and 3.59±0.53 µM more than etoposide. In addition, (-)-kusunokinin showed less cytotoxic to normal L-929 cells with IC₅₀ values of 69.40±0.87 µM. Then, the molecular docking analysis showed inhibitory effect of (-)-kusunokinin against FMS kinase protein with strong binding energy value of -11.53 kcal mol⁻¹ and inhibition constant value of 3.54 nM, which better than pexidartinib, a FMS known inhibitor. Finally, (-)-kusunokinin at dose 7.0 mg/kg.BW, 14.0 mg/kg.BW and combination of 7.0 mg/kg.BW (-)-kusunokinin with 0.5 mg/kg.BW doxorubicin induced cell death in tumor tissues and caused tumor inhibition with the suppression rate at 56.1, 68.9 and 82.9% respectively. Moreover, (-)-kusunokinin reduced cancer progression through down-regulation of c-myc, CDK1 and cyclin B1 proteins.

Conclusion: In conclusion, our data suggest that (-)-kusunokinin could bind to FMS kinase receptor protein and regulated cellular proliferation and cell cycle in breast cancer cells and rat models.

Recent Publications:

1. Srisawat T, Sukpondma Y, Chimplee S, Kanokwiroon K, Tedasen A, Graidist P (2014) Extracts from Vatica diospyroides type SS fruit show low dose activity against MDA-MB-468 breast cancer cell line via apoptosis action. Bio Med Research International; article id: 479602.
2. Sriwiriyan S, Tedasen A, Lailerd N, Boonyaphiphat P, Nitiruangjarat A, Yan D, Graidist P (2016) Anti-cancer and cancer preventive effects of a piperine free Piper nigrum extract on N-nitrosomethylurea induced mammary tumorigenesis in rats. Cancer Prev Res; 9: 74-82.

Biography

Aman Tedasen is currently working as a Post-doctoral Researcher at Prince of Songkla University, Thailand. His research interest has focused on developing effective treatment strategies from herbal medicine for breast cancer.

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