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β- caryophyllene, a natural sesquiterpene isolated from agar wood inhibits growth and metastasis of human colorectal cancer by modulation of multiple targets *in vitro* and *in vivo*

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Objective: Our study focuses upon colon cancer, due to its high rate of morbidity and mortality worldwide. Looking for new agents from plants which are safe, available and effective have accelerated recently. We investigated the effect of β-caryophyllene (BC) on the mechanism of cell death, inhibition of metastasis and induction of colon tumor in nude mice model.

Methods: The structure of β-caryophyllene was elucidated using FT-IR, 1H and 13C NMR and MS spectral. Anti-colon cancer effect was investigated on HCT 116 human colorectal carcinoma cells including cytotoxicty, anti-tumorigenicity and anti-metastatic. In addition, xenograft model was conducted in orthotopically implanted colon cancer cells in nude mice. The mechanism of the cell death have been assessed through disruption of mitochondrial membrane potential, DNA fragmentation, ultra-structural micrographs using (TEM) and apoptotic antibodies array.

Results: We found that BC inhibited the proliferation of colon cancer cells (median inhibitory concentration 9.5±1.0μg/ml), due to induction of the mitochondrial pathway of apoptosis. Interestingly, the main three steps in tumor metastasis including, cell invasion, cell migration and clonogenicity were significantly obstructed .Transmission electron microscope reveal further supportive information on the typical singe of apoptosis morphological changes including nuclear shrinkage, chromatin condensation and nuclear fragmentation. Administration of BC (200,100 and 50 mg/kg/day) dose-dependently inhibited the growth of colon cancer in an orthotopic model. Tumor histology revealed significant reduction in vascularization. Bioluminescence images of implanted tumors with pro-sense and angio-sense probes were illustrated by fluorescence molecular tomography (FMT)

Conclusion: Collectively, our results reviled a new mechanism of action of β-caryophyllene and suggest that it may be a potential chemotherapeutic agent selectively against colon cancer.

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In Silico Test, Sintysis and Analog Anti Folat Activity Test in the HeLa Cell as Anti Servics Cancer

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Indonesia, each year approximately 15,000 new cases of cervical cancer and 7,500 of them lead to death. In cancer cells was found that excess folic acid needs. Have been many analog of folic acid (antifolate) is used as the analog cancer chemotherapy but still have considerable side effects. So it is necessary to modify the folic acid molecule to produce another analog that is expected to provide an optimal activity but have low toxicity. Folic acid modification begins with drafting a compound where folic acid is added the groups which have lipophilic properties, electronic and steric certain. Then tested *in silico* to predict bond strength analogous to receptors. Then do the synthesis of these compounds with Schotten-Baumann method and the its analog results tested the activity in cervical cancer cells with *in vitro* assays in HeLa cells that compared to the positive control (methotrexate) with MTT assay method. Results from *in silico* test shows modified compounds have lower scores rerank (potent). Results synthesis proved by infra red spectrophotometric and h-nmr spectrophotometric test. the compounds synthesized tested with MTT assay test that compared with methotrexate at a level of 250 ppm of obstacles 8.1 (compounds synthesized) and 83.1 (methotrexate). This research resulted in 2-N- (benzoyl) –folate acid as antifolate that proved to be more potent.

Keywords : Cervics Cancer, Folat Acid, HeLa Cell

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