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SYNTHESIS OF THIOUREA DERIVATIVES OF ETHYL P-METHOXYCINNAMATE ISOLATED FROM KAEMPFERIA GALANGA AND THEIR CHEMOPREVENTIVE ACTIVITIES AGAINST FIBROSARCOMA IN MICE

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ABSTRACT

Cyclooxygenase-2 (COX-2) plays important role in acute and chronic inflammation, tumor pro-gression and metastasis in various cancer types, including fibrosarcoma. Therefore, inhibiting COX-2 could stop the progression of cancer. Ethyl p-methoxycinnamate, major ingredient of Kaempferia galanga rhizome, has been reported not only as analgesic – anti inflammatory repressed cyclooxygenase, but also inhibits tumor cell proliferation of mouse epidermis and papilloma. In this study, ethyl p-methoxycinnamate was used as starting material to produce thiourea derivatives as cancer chemopreventive agents. Thiourea derivatives, namely N-(phenyl)-N'-(p'-methoxyphenyl)thiourea,N-(p-methylphenyl)-N'-(p'-methoxyphenyl)thiourea and N-(p-chlorophenyl)-N'-(p'-methoxyphenyl)thiourea were synthesized by substitution and addition the acyl halide with ammonium thiocyanate and commercial amines. The synthesis products were confirmed by UV-Vis, FTIR, 1H-NMR, 13C-NMR and HRMS spectroscopic methods. Their activities were tested in vivo using mouse model against carcinogenesis of fibrosarcoma at dosage 40 mg/kg, which were given daily for thirty days. Celecoxib was used as positive control and one group without treatment as negative control. Carcinogenesis in fibrosarcoma was induced by 0.3% benzo(a)pyrene injected subcutaneously of mice, which was given five times, once every two days. Our results show that carcinogenesis process of fibrosarcoma can be inhibited by all synthesized compounds. In silico analysis of inhibition mechanism of synthesized compounds against COX-2 was done using AutoDock Vina program. Our docking results show that all synthesized compounds have better interaction with COX-2 than that of ethyl p-methoxycinnamate.