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Piper betle leaf extract enhances the cytotoxicity effect of 5-Fluorouracil in inhibiting the growth of HT29 and HCT116 colon cancer cells

Key words: Piperaceae, *Piper betle* L, 5-fluorouracil, isobologram analysis, herb-drug interaction

- 5-Fluorouracil (5FU) is a standard chemotherapeutic drug used to treat colorectal cancer. However it rapidly developed acquired resistance and with short half-life.

- Combination anti-cancer treatments using the active compounds from plant extracts enhance anticancer treatment with minimum cytotoxicity to the host cells.

- *Piper betle* (PB) is a well-known ethnomedicinal plant riches with hydroxychavicol (HC) has showed to enhance the anti-cancer drug cytotoxicity.

- This study is to determine the combination effect of *Piper betle* (PB) and 5-fluorouracil (5FU) in enhancing the cytotoxic potential of 5FU in inhibiting the growth of colon cancer cells.

- Apoptosis feature of the combination 5FU and PB treated colon cancer cells lines were reveled by Annexin V/PI staining. PB-5FU interaction was elucidated by isobologram analysis

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Results

	Treatment	IC50	Effect time
Drug-resistant colon cancer cells, HT29	PB	200.0 μg/mL	36-h
	5-FU	130.0 μM	72-h
	PB + 5-FU	500.0 μg/ml PB + 12.5 μM 5-FU	24-h
Colon cancer cells, HCT116	PB	187.5 μg/mL	36-h
	5-FU	12.5 μM	72-h
	PB + 5-FU	500.0 μg/mL PB + 12.5 μM 5-FU	24-h

- Both cell lines treated with 5FU or PB alone induced a greater apoptosis effect compared with the combination treatment.

- Isobologram analysis indicated PB and 5FU interacted synergistically and antagonistically in inhibiting the growth of HT29 cells and HCT116 cells, respectively. However combination of PB active compound (HC), 4-allypyrocatechol showed antagonistic interaction with 5-FU on HT 29 cells. Synergistic effect of PB extract and 5FU on HT29 cells may not solely be due to its major active compound, HC.

- In the presence of PB, a lower dosage of 5FU is required to achieve the maximum drug effect in inhibiting the growth of HT29 cells. However, PB did not significantly reduce 5FU dosage in HCT116 cells. The result showed this interaction may not solely contribute to the apoptosis pathway.

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