

## Chemopotential Features of *Annona muricata* Leaves for Colorectal Neoplasm

Murdani Abdullah

Division of Gastroenterology, Department of Internal Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

Colorectal cancer was an emerging disease in the world with increasing prevalence over the year. According to the recent data, colorectal cancer was ranked second in males and third in female from all prevalence of cancer worldwide.<sup>1</sup> Incidence of colorectal cancer in Indonesia is 17.2 per 100,000 population with high mortality rate 12.9 per 100,000 population.<sup>2</sup> The increasing trend is need to be balanced with appropriate and efficacious treatment and may need any adjuvant to the available treatment such as surgery, radiotherapy or chemotherapy.

Indonesia is one of the tropical country with wide variety of biodiversity especially of herbal and natural compound.<sup>3</sup> Herbal or traditional medicine was commonly used by the native Indonesian and believed as the traditional drug in rural as well as urban areas.<sup>4</sup> Many studies of the natural compound have been conducted and have scientifically potential efficacy for medical uses. However, the study of this traditional material was limited and there were many of the natural compound that may be scientifically benefit but have not been studied yet.

*Annona muricata* (*A. muricata*) or soursop leaves was one of the natural resources that commonly used for traditional treatment. In addition, several studies of *A. muricata* suggested that the leaves of this compound had antibacterial, antiproliferative, antidiabetic, anti-inflammatory, antioxidant and other beneficial effects.<sup>5</sup>

Previous *in vitro* study from Indrawati et al demonstrated the potential chemotherapeutic effects. Ethanol-soluble fraction of water extract of *A. muricata* (ESFAM) extract had cytotoxicity effects on DLD-1 and COLO-205 which were colorectal cancer cell lines. The inhibitory concentration (IC<sub>50</sub>) of ESFAM was found lower than 5-fluorouracil as positive control and placebo as negative control (20.59 µg/mL vs 277.7 µg/mL and 654.9 µg/mL, respectively). *Ex vivo* experiment also demonstrated that subjects' serum could stimulate the activities of caspase-8 and caspase-9 on DLD-1 cell lines. Caspase-8 and caspase-9 known as a marker of cancer apoptotic cycle.<sup>6</sup> Abdullah et al also found that *A. muricata* has potential pro-apoptotic and anti-

proliferative by enhancing the expression of caspase-3 on COLO-205 colorectal cancer cell line and down-regulate COX-2 expression on HT-29 colorectal cancer cell line.<sup>7,8</sup>

*In vivo* study from Moghadamtousi et al showed ethyl acetate extract of *A. muricata* leaves showed down-regulation of proliferating cell nuclear antigen, a marker of cell proliferation, and also Bcl-2. *A. muricata* also up-regulated Bax protein which was a pro-apoptotic that mediates the leakage of pro-apoptotic factors including cytochrome c, Ca<sup>2+</sup>, and Smac/DIABLO.<sup>9</sup>

Indrawati et al then continued their study earlier and reviewed the safety profile of one of the natural sources that may have potential effects on various disease treatment especially in colorectal cancer. Indrawati et al using the extract of *A. muricata* or soursop leaves and fractionated using ethanol to produce the ethanol-soluble fraction of water extract (ESFAM). This ESFAM contains 0.36% acetogenin, in which was the active compound that may has benefit for chemotherapy effect.<sup>10,11</sup>

This study is considered as Phase I clinical trial of *A. muricata* extract with 30 patients of colorectal cancer patients with previous complete resection of the primary tumour was included in the trial. Subjects randomly allocated in either supplementation of 300 mg ESFAM or maltose as placebo in the form of capsule and administered after breakfast for as long as 8 weeks with mean 56 days taking the supplements.

Indrawati et al found that *A. muricata* extract as the form of 300 mg ESFAM capsule was considered safe in administration in human subjects. No statistical significance was observed in the chemical marker such as hepatic function, kidney function, and haematological parameter after the prescription of the extract. Only 6.7% complained intolerant side effects. However, the authors did not mention the side effects occurred in the subjects. Presumably, the side effects may be harmless and suggested acceptable for patients taking the supplements.

This finding could escalate further studies using the extract of *Annona muricata* leaves especially in colorectal cancer treatment. There may be benefit of this compound for its chemopotential effects in colorectal cancer.

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