Reviewer's report

Title: alpha-Mangostin extracted from the pericarp of the mangosteen (Garcinia mangostana Linn) reduces tumor growth and lymph node metastasis in an immunocompetent xenograft model of metastatic mammary cancer carrying a p53 mutation

Version: 1 Date: 14 February 2011

Reviewer: Yian Wang

Reviewer's report:

This is a review on the manuscript submitted to BMC Medicine by Masa-Aki Shibata, Munekazu Inuma, Junji Morimoto, Hitomi Kurose, Kanako Akamatsu, Yasushi Okuno, Yukihiro Akao, and Yoshinori Otsuki. The title of the manuscript is "alpha-Mangostin extracted from the pericarp of the mangosteen (Garcinia mangostana Linn) reduces tumor growth and lymph node metastasis in an immunocompetent xenograft model of metastatic mammary cancer carrying a p53 mutation".

Summary:
In this manuscript, Masa-Aki Shibata et al. reported their investigation of a-Mangostin isolated from mangosteen for its antimetastatic activity in mammary cancers carrying a p53 mutation with both in vitro and in vivo approaches. In in vivo studies, they found significant effects of a-Mangostin at the dose of 20 mg/kg/day on survival rates, tumor volume increases, lymph node metastasis, tumor cell apoptosis, microvessel density, as well as number of dilated lymphatic vessels containing intraluminal tumor cells. In their in vitro studies, they found significant effects of a-Mangostin on mitochondria-mediated apoptosis, G1-phase arrest, etc. Also, they investigated alterations in Akt phosphorylation by a-Mangostin with both in vitro and in vivo systems. Their analysis showed that the expression of phospho-Akt-Thr308, but not phospho-Akt-Ser473, was significantly lower in mammary tumor cells treated with a-Mangostin. They conclude that [1] the findings may have important clinical applications, as lymph node involvement is the most important prognostic factor in breast cancer patients; and [2] a-Mangostin may be useful as an adjuvant therapy or complementary alternative medicine and for the chemoprevention of breast cancer development.

General Comments:
The preclinical identification of agents of potential use for preventing tumor metastasis has proven to be a difficult task. In that regard, the observation that a-Mangostin significantly increases survival rate and significantly suppresses tumor volume increases, suppress multiplicity of lymph node metastasis is encouraging.

However, this reviewer would have more enthusiasm for a-Mangostin if it had
been shown to reduce both mammary tumor volume and mammary tumor metastasis in a primary mammary tumor model(s).

Overall, the study is adequately designed, the experiments appear to have been appropriately performed, and the data adequately analyzed. Although the studies reported are not considered to be original or novel, the authors are at most descriptive in nature with quite extensive mechanistic insights. The authors are known for their extensive experiences in breast cancer studies. The demonstration of inhibitory activities of a-Mangostin by suppresses tumor volume increases, suppress multiplicity of lymph node metastasis is considered to be significant.

The findings are of some importance because they may serve as basis of selecting a-Mangostin for future therapy and chemoprevention of breast cancer. The writing is acceptable.

Specific Comments:

Page 2: to this reviewer, the “background” and “Methods” sections in the Abstract are not really completed.

Page 6 (middle): what is the nature of the animal used?

Page 6: The description of cell culture conditions was un-necessarily repeated in the 2nd paragraph and the last paragraph.

Page 9: what is the meaning of “HPP”?

Page 10: The authors used subcutaneously implanted mini-osmotic pumps to deliver a-Mangostin to the treated mice. What about the control mice? Did they receive any implant? As we know that physical stress is a factor on tumor development and progression.

Page 18: The authors observed p-Akt-Thr308, but not the p-Akt-Ser473, was significantly lower in mammary tumor cells treated with a-Mangostin. However, the authors did not provide more in-depth insights to explain why.

The authors used “a mouse metastatic mammary cancer model carrying a p53 mutation”. What is the specific mutation in the p53? Also, the authors should describe briefly the role of mutant p53 in breast cancer.

There are two different cell lines used in this study. It is not easy to track on what cell line was used in what assay.

The authors stated that “the number of dilated lymphatic vessels containing intraluminal tumors cells was significantly lower” in a-Mangostin treated mammary tumors. However, to this reviewer, it is mis-leading in Figure 6I and Figure 6J.

Also, in Figure 6, the quality of C and D specifically is very poor as there is no clear structure of tissue can be seen. It seems that the areas taken for Figure 6C and 6D are quite different from rest of panels in this figure.
Similar to Figure 6C and 6D, there is no clear tissue structure in the Figure 7C-F.