Reviewer's report

Title: Induction of Apoptosis in Estrogen Receptor-Negative Breast Cancer, MDA-MB231 Cells, by Ethanolic Mango Seed Extract through Mitochondrial Cytochrome C Release

Version: 2
Date: 16 January 2015

Reviewer: Mariano Bizzarri

The manuscript "Induction of Apoptosis in Estrogen Receptor-Negative Breast Cancer, MDA-MB231 Cells, by Ethanolic Mango Seed Extract through Mitochondrial Cytochrome C Release" provides convincing data suggesting that Mango extract induce a significant increase in apoptotic rate in breast cancer cell lines. Authors thoroughly investigated both extrinsic as well the intrinsic apoptotic pathway, evidencing that increase in programmed cancer cell death is presumably triggered by a "paradoxically" increase in ROS release and further p53 activation.

Despite these interesting data, I have some major questions:

1. first of all, the overall value of those results would be greater if another cancer cells line (i.e., MCF-7) had been studied.

2. Secondly, the potential mechanism of extracted putative anticancer compounds from Mango is loosely ascribed (in the Introduction section) to their antioxidant mechanism of action. Several components of that extraction mixture may presumably have an antioxidant property, as demonstrated for other fruit extracts (namely grape seed). However, even that antioxidant property may undoubtedly exert a priceless effect in preventing cancer onset, it is doubtful that antioxidant process may support an anticancer effects. Indeed, the data showed by the study evidenced Mango extracts exert - "paradoxically" - a pro-oxidant effect, leading thus to an increase in cytochrome-c release and in MDA products. The paradoxical pro-oxidant effect of well-known "anti-oxidant" compounds it is indeed increasingly appreciated by the scientific literature and suggest that these substances may act differently according to the actual context (i.e., depending on the true nature of tested cell lines). the Authors may refer to some scientific reviews dealing with that subject (for instance: Dinicola S. et al., Anticancer Effects of Grape Seed Extract on Human Cancers: A Review, J Carcinog Mutagen 2014, S8). I reckon that this issue is a very pivotal one and should be properly addressed both in the different sections of the manuscript (namely Introduction and Discussion), as well as in the title. Additionally, the meaning of the paper would benefit by evaluating if a “true” antioxidant substance (like N-acetyl-cysteine) could inhibit the pro-oxidant effects (and the resulting apoptotic activity) induced by Mango extracts. I suggest that such experiment would be performed in order to strengthen the overall value of the this study.
Minor observations:
1. In the Introduction, breast cancer is credited as having “the highest mortality rate”. This is not exact: many other cancers showed an far greater mortality rate than breast tumors
2. Manuscript should be amended from some errors and carefully revised by a native-speaking English.

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests