Reviewer's report

Title: Frankincense oil derived from Boswellia carteri induces tumor cell specific cytotoxicity

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Reviewer: Monica Liebert

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This report takes a novel approach to evaluation of natural products for cancer therapy by utilizing gene array and bioinformatics analysis. The authors are clear in the introduction on the goals (and those potential goals not included in the study). The methods are well described and appropriate. The basic finding, that this agent causes cell death in J82 bladder cancer cells while sparing UROtsa “normal” urothelial cells, is performed in a traditional format for cytotoxicity. Rapid cell death is noted with the J82 cells, although not through apoptotic death, while the UROtsa cells appear to be spared. Gene analysis reveals a number of possible cellular pathway changes that may contribute to the effect of the frankincense oil.

The paper is well written and well presented. The cytotoxicity data (Figure 2) are presented in a relatively unusual fashion (“fold change in cell viability”). A more traditional percent surviving or killed cells would be more accessible and comparable for the literature. Since the authors don’t see DNA laddering, the assumption is that the cell death is not due to apoptosis. However, the timing of evaluation can be critical in for apoptosis analysis. If not apoptosis, what type of cell death is involved? Necrosis or autophagy are two other possibilities which could be indicated or excluded via appropriate assays. Since one of the genes upregulated 2-fold is related to autophagy (ATG2, mentioned in the discussion) that might implicate autophagy as a mechanism. Unfortunately, another autophagy gene, ATG5, is downregulated by the same amount. The reason to explore this effect further is to understand the potential interaction and/or classification of this agent with others currently in use (i.e., intravesical chemotherapeutic agents such as mitomycin C or BCG). A weakness in the study is that only two cell types were evaluated. Since the normal cells are apparently spared, and the tumor cell line killed, the next logical step is evaluation in other bladder cancer cell lines. Additionally, animal studies will need to be performed to confirm the lack of toxicity on normal urothelial cells. Although studying only two cell types is a weakness, the novelty of the agent and the approach using gene arrays make the report a valuable contribution to the literature.

The gene analysis is intriguing. It is not unexpected using an unpurified “natural” agent, there are multiple pathways involved in the response. It would be hard to pinpoint one gene pathway or mechanism. However, the Gene Ontogeny classification is relegated to supplemental data, which may not be as helpful as a
summary table in the paper itself. Many publications using GO classification provide just numbers of genes in each category to allow the reader to evaluate how the pathways are perturbed. Inclusion of such a table would strengthen the paper. The specific gene tables from the GO analysis should be retained in supplemental data.

The introduction is especially well presented, and the conclusions are sound based on the data presented. The title and abstract are appropriate and clear. The authors present the basis for the work in both the introduction and discussion.

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

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare I have no competing interests.