Reviewer’s report

Title: Piper betle induces phase I & II genes through Nrf2/ARE signaling pathway in mouse embryonic fibroblasts derived from wild type and Nrf2 knockout cells

Version: 2 Date: 5 August 2013

Reviewer: Scott A Reisman

Reviewer’s report:

The article has been greatly improved. However, there are still issues that need to be addressed before I can support publication.

Major Comments:

The authors did not adequately address the request for additional Nrf2 target measurements. Ho-1 and Sod1 are not the best for evaluation of Nrf2 engagement. Even if western blots cannot be performed, which they should be for most targets, mRNA expression of a wide variety of Nrf2 targets would add substantial value.

Minor Comments:

1. The statement is made that "Aqueous extract of PB leaves provides better protection against tissue lipid peroxidation in diabetic rats." Please indicate what the extract is better than or simply state that the extract decreases lipid peroxidation in tissues (which tissues?).

2. Please provide references for the source Nrf2-null mice (multiple lines exist) and Nqo1-ARE sequence used.

3. Because of the known differences between cancer and "normal" cells in sensitivity to ROS, it is suggested that comparisons be made in models where normal cells are used when describing MEF cell sensitivity instead of references 22 and 23.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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

Declaration of competing interests:

I am employed by and have a financial stake in Reata Pharmaceuticals, a company engaged in the development of Nrf2 activators for the marketplace.