Reviewer's report

Title: Identification of Molecular Pathways Affected by Pterostilbene, a Natural Dimethylether Analog of Resveratrol

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Reviewer: Gustavo Goldman

Reviewer's report:

This manuscript aims to identify the cellular pathways affected by pterostilbene, a naturally occurring phenolic compound produced by agronomically important plant genera such as Vitis and Vaccinium. These analysis were performed by using transcript profiling studies employing the model yeast Saccharomyces cerevisiae. Several genes and pathways were identified as modulated by pterostilbene. The mRNA accumulation of some of these genes was validated through other methodologies, such as real-time RTPCR, and growth of deletion strains in the presence of pterostilbene. The results were compared and several hypotheses were proposed for the influence of pterostilbene on the metabolism. The manuscript is well written and experiments well performed. I am not surprised the deletion strains, except pdr3 delta, have not shown the expected behavior based on the expression analysis in the presence of pterostilbene. Actually, there are few examples now in the literature showing this discrepancy between expression and deletion analysis and they should be discussed in this manuscript. It would be more interesting to see if the metabolic pathways are really involved in pterostilbene mechanism of action by alternative ways. Thus, I would like to suggest some experiments that could improve the manuscript.

1) Pterostilbene up-regulated several genes involved in sterol, phospholipid and sphingolipid metabolism, including genes involved in the regulation of lipid metabolism. These results suggest that possibly there is an increased susceptibility to azoles since the synthesis of ergosterols is probably increased. This could easily be verified by a synergism between fluconazole (or lovastatin) and pterostilbene. Additionally, increased expression of genes involved in ergosterols and phospholipids also could affect the location of lipid rafts in the budding neck. Experiments with filipin after induction with pterostilbene could bring some light to this hypothesis.

2) It is interesting the observation that genes involved in methionine metabolism have decreased mRNA accumulation. This also suggests that when S. cerevisiae is exposed to pterostilbene and analogues of sulfur synthesis, such as selenate, it will be probably observed some growth inhibition synergism.

Minor comments:

a) Results, page 10, line 11, typo: â##â#¦knownâ#¦;â##;
b) It would be really interesting to see a correlation analysis between the microarray and real-time RTPCR expression data;

c) Results, page 14, line 16, typo: â##â#|anomaliesâ#|â##;

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.