Reviewer's report

**Title:** Neutral sphingomyelinase 2 modulates cytotoxic effects of protopanaxadiol on different human cancer cells

**Version:** 3  **Date:** 27 February 2013

**Reviewer:** Zhi-Xiang Xu

**Reviewer's report:**

Dr. Park and his colleagues reported an intriguing finding that protopanaxadiol (PPD) induces cytotoxicity on human cancer cells through activating neutral sphingomyelinase 2 (nSMase 2) hydrolyzing membrane sphingomyelins into proapoptotic intracellular ceramides via the disruption of lipid rafts, which provides a valuable rationale for its clinical application as an adjunct in cancer chemotherapies.

It is a well-designed, conducted, and organized investigation. The authors have provided convincing evidence demonstrating that PPD induces cancer cell death through activation nSMase 2 by increasing intracellular ceramides to enhance apoptosis. It is acceptable currently. The authors are suggested to perform more mechanistic investigations in the future addressing how PPD affects the integrity of lipid rafts, is the activation of caspase-8 by PPD dependent on cell death receptors on cellular surface? Are intracellular membrane structures, such as ER, also affected by PPD? etc.

Discretionary Revisions

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

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