Activation of the Hepatocyte Antioxidant Response by Kava Secondary Metabolites

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Although used by Pacific Islanders for thousands of years, Kava hepatotoxicity has been a concern. The purpose of this project was to determine which of the Kava secondary metabolites activate the antioxidant or heat shock response systems in human hepatocytes. Cellular viability in HepG2 liver cells exposed to oxidative stress with the identified kava metabolites was then evaluated. The experimental question was which kava secondary metabolites are activated and what cellular responses do they exhibit? The hypothesis was that some of the Kava's compounds could be precursors for metabolic activation as measured by HSF-1 or Nrf-2 dependent gene expression. First, total mRNA extraction and reverse transcription to cDNA with real-time PCR of the four selected kavalactones and the two flavokawains (FKA and FKB) was done to see if activation of the heat shock factor or antioxidant response occurred. The data showed the heat shock response was not activated but the antioxidant response, as indicated by heme-oxygenase-1 (HO-1), was activated by both FKA and FKB. Both FKA and FKB were then used to collect total and nuclear proteins via Western blot to analyze the amount of antioxidant gene expression. Finally, a cellular viability assay was used to determine the impact of FKA/FKB on hepatocyte resistance to oxidizing agents. The hypothesis was supported because FKA activated HO-1, which activated Nrf-2 gene expression. The activation of the NrF-2 protein provided protection for HepG2 cells, as shown by a 70% viability after exposure to oxidative cell stress. Future research on the use of kava and FKA has potential significance to support liver health in kava consumers, as well as other types of human aging diseases (Parkinsons) that may benefit from antioxidants.