ELIO F. DELATORE III, ZACHARY CLARK, MEGAN AYALA, & JOSEPH HORZEMPA. Department of Biomedical Sciences. West Liberty University. West Liberty, West Virginia. The Efficacy, Toxicity & Pharmacology of Dillapiole: a potential new treatment for Tularemia

Francisella tularensis, a highly infectious bacterium, is the causative agent of Tularemia (rabbit fever). Categorized by the Center for Disease Control and Prevention as a Category A bioterrorism agent, *Francisella tularensis* is of the highest level of concern. Previously, we identified that dillapiole, a compound extracted from fennel, dampens *F. tularensis* virulence gene expression. While having no apparent effect on the viability of *F. tularensis*, treatment with this compound leads to reduced bacterial viability during *in vitro* infection of THP-1 monocytes and RAW 264.7 macrophages. In this study, we sought to determine if dillapiole exhibited a therapeutic effect in vivo, and to characterize the toxicity and pharmacology of this compound. In a murine tularemia model, female mice treated with dillapiole trended toward increased survival compared to those treated with the vehicle. However, dillapiole- or vehicle-treated male mice showed increased mortality compared to the females, suggesting gender-specific differences in the murine immune response to *F. tularensis.* Dillapiole was not toxic to HEK-293 cells in vitro, nor was this compound toxic to primary human hepatocytes when tested up to a concentration of 11 μg/ml (50 μM). Dillapiole was shown to be relatively stable in human, rat, and mouse plasma with a half-life greater than 120 minutes in all cases. However, this compound showed moderately high binding to plasma proteins (86% in human plasma and 75% in mouse plasma). In addition, while dillapiole showed moderate clearance by human and rat liver microsomes, mouse liver microsomes exhibited high clearance. Collectively, these data could explain the minimal efficacy observed in vivo. Therefore, future investigations should involve the rat infection model to determine the potential efficacy of dillapiole as a novel treatment for tularemia.