Mechanism of Action of American Ginseng and its Components in the Treatment of Ulcerative Colitis

Anusha Chaparala

Inflammatory bowel diseases (IBD), mainly ulcerative colitis (UC), Crohn’s disease (CD), are chronic, idiopathic, inflammatory diseases of the gastrointestinal tract affecting millions of people worldwide. The incidence of IBD is steadily increasing in the modern world due to changes in dietary habits and other environmental influences that originated from industrialization. Aside from severely affecting the quality of life of the patients, IBD also increases the risk of developing colorectal cancer (CRC). This makes it imperative to find a treatment that not only treats colitis but can also act as a chemopreventive agent. Current medications help patients cope with the symptoms and induce temporary remission, but are paired with a risk of serious side effects and disease becomes refractory. Many patients, therefore, turn to unconventional treatments for relief and plant-based products provide a safe, alternative option. Our lab has previously shown that AG treats colitis and prevents colon cancer in mice. This indicates the potential for AG to become part of mainstream medicine like other drugs that have natural antecedents. Drug discovery from plant products involves phytochemical and biological characterization of plants used in alternative medicine. This dissertation aims to address these issues by identifying the bioactive component of AG and elucidating the mechanism of action in the treatment of UC.

We used bioassay-guided fractionation to identify the most potent fraction of AG. A hexane fraction of AG (HAG) has shown remarkable anti-inflammatory and anti-cancer properties both in vitro and in vivo. Panaxynol (PA), a polyacetylene that is the most abundant compound in this fraction, effectively suppressed DSS induced colitis in mice and shows potential as a chemopreventive agent. PA’s mechanism of action involves targeting macrophages (mΦ) for DNA damage and apoptosis. Because AG has been shown to decrease oxidative stress we hypothesized that AG, HAG, and PA treat colitis by activating Nrf2, an initiator of antioxidant response. AG, HAG, and PA decreased oxidative stress and activated the Nrf2 pathway in vitro and in vivo. Accordingly, in vivo experiments indicate that AG, HAG, and PA were not very effective in the treatment of DSS induced colitis in Nrf2 knockout mice.

We further delineated the mechanism of action of AG in the absence of inflammation using gene expression profiling of primary peritoneal mΦ by microarray. We found that AG and its compounds showed distinct immunomodulatory properties, as shown by the activation of both pro-inflammatory cytokines and anti-inflammatory molecules. These results will bring AG a step closer to being used as a conventional drug for the treatment of colitis and pave the way for its use in the treatment of other inflammatory and autoimmune diseases with a similar genesis.