MicroRNAs (miRNAs) are small noncoding single stranded RNAs that are considered master regulators of gene expression. They are also an emerging class of therapeutic agents with significant potential for the prevention and treatment of many diseases, including cancer. Many different forms of cancer are associated with loss or reduced accumulation of one or more miRNAs that function as tumor suppressors. In animal models, restoration of missing tumor suppressor miRNAs prevents the initiation, progression and/or spread of the disease. However, the current absence of an efficient method for delivery of therapeutic miRNAs is a critical barrier to their use. The research in this thesis has tested a novel chemopreventive strategy for miRNA replacement therapy based on ingestion of plant matter that has been bioengineered to produce mammalian tumor suppressor miRNAs. The work builds on the Vance lab’s promising pilot study showing that oral administration of plant RNA spiked with a cocktail of three tumor-suppressor miRNAs (miR-34a, -143, and -145), synthesized with the 3’-methylation characteristic of plant miRNAs, has significant chemopreventive activity in the ApcMin/+ mouse, a well-established animal model of colon cancer. Based on this work, Arabidopsis thaliana was bioengineered to produce the same three tumor suppressor miRNAs used in the earlier study. This required devising strategies to engineer miRNAs that are not the standard 21-nt size of most plant miRNAs. In a small pilot study using these plant-made tumor suppressor miRNAs, we found that ApcMin/+ mice that were fed a diet containing the transgenic Arabidopsis tissue developed significantly fewer tumors than mice fed a control diet that was calorically and nutritionally matched, but did not contain plant tissue. Although the results using this delivery method were promising, the approach was limited due to the feeding preferences of the mice. Thus, subsequent work focused on a strategy to deliver high levels of plant-made miRNAs using packaging into plant exosome-like nanoparticles, which are taken up by the mammalian digestive tract after ingestion. For plant exosome-like nanoparticles to be effective in future studies, techniques for enhancing the loading of bioengineered miRNAs were developed. Work reported here points to the importance of the identity of the 5’ nucleotide of the engineered miRNA for efficient loading into plant exosome-like nanoparticles for subsequent delivery by ingestion.