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# Suppression of Colon Carcinogenesis by Bioactive Compounds Found in Grapefruit

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## ABSTRACT

Recent epidemiologic studies show that consuming a diet high in fruits and vegetables is protective against many types of cancers, including colon cancer.<sup>1-3</sup> This poster examines compounds found in grapefruit as chemopreventive agents using azoxymethane-induced rats. Additionally, isolated compounds are compared with both natural and irradiated grapefruit pulp in their effectiveness at decreasing incidence of aberrant crypt foci in colon tissue. The results indicate that although each experimental diet showed an improvement over the control diet, natural grapefruit and limonin may serve as better chemopreventive agents compared to irradiated grapefruit and naringin.

## OBJECTIVES

- Examine the literature regarding compounds such as limonin and naringin
- Explore their effects on colon carcinogenesis
- Understand the mechanism by which colon carcinogenesis is influenced by these compounds
- Educate the public on the importance of incorporating fresh fruits and vegetables into the diet.

## BACKGROUND

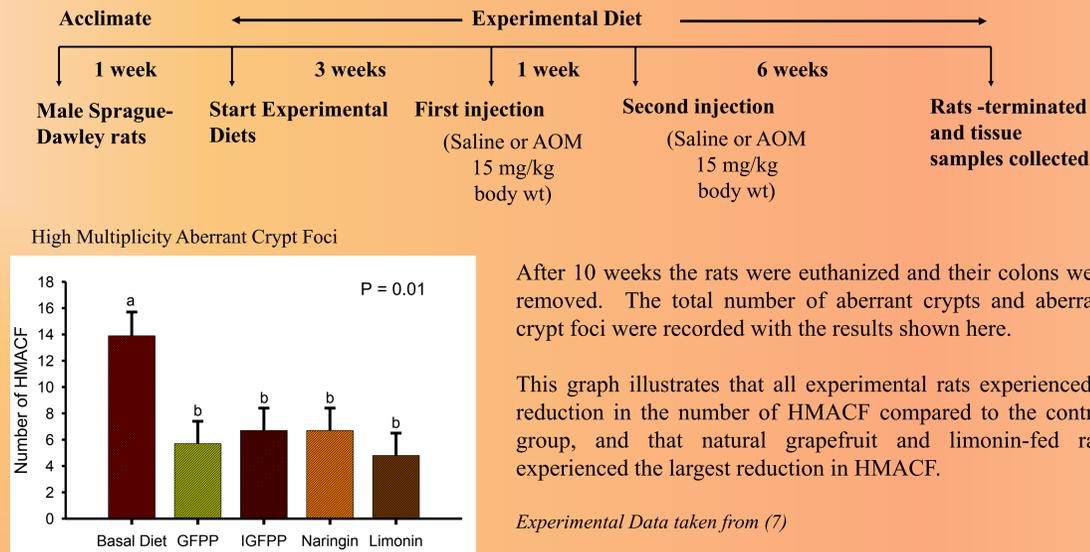
- Colon cancer is the second leading cause of death from cancer in the United States for both men and women.<sup>4</sup>
- More individuals die from colon cancer each year than from breast cancer and AIDS combined.<sup>4</sup>
- Citrus fruits/grapefruit have been shown to reduce the damage to colon cells from azoxymethane (AOM), a carcinogenic compound known to induce colon cancer.<sup>5,6</sup>
- In this poster we will examine the relationship between two types of grapefruit (natural and those treated with irradiation), two isolated compounds found in grapefruit (limonin and naringin), and their relationship to colon carcinogenesis.

## EXPERIMENT

100 male Sprague-Dawley rats  
AOM (15 mg/kg body wt) or Saline

20	20	20	20	20
Basal	Natural Grapefruit (13.7 g/kg)	Irradiated Grapefruit (13.7 g/kg)	Naringin (200 mg/kg)	Limonin (200 mg/kg)

Five groups of rats were formed based on diet: control, natural grapefruit, irradiated grapefruit, naringin, and limonin. Each group was then further divided with half of each group receiving subcutaneous azoxymethane injections and the other half receiving injections of saline.



After 10 weeks the rats were euthanized and their colons were removed. The total number of aberrant crypts and aberrant crypt foci were recorded with the results shown here.

This graph illustrates that all experimental rats experienced a reduction in the number of HMCAF compared to the control group, and that natural grapefruit and limonin-fed rats experienced the largest reduction in HMCAF.

## PHYSIOLOGY

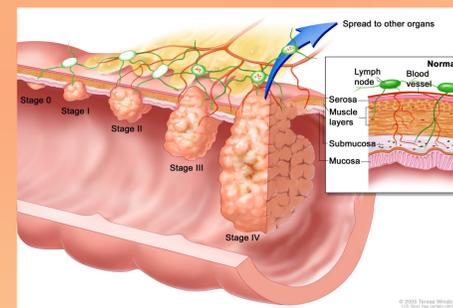
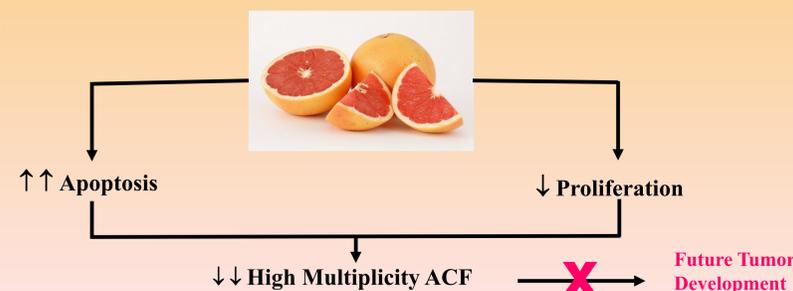
The colon consists of a single epithelial layer comprised of many crypts, the organ's basic functional unit. In a normal crypt stem cells at the base of the crypt differentiate into new colon cells. Within days these cells mature and are either sloughed off into fecal matter or subjected to programmed cell death, or apoptosis. This continuous death and regeneration of cells is essential to colon health.

Aberrant crypt foci (ACF) are clusters of abnormal tube-like glands in the lining of the colon. ACF form before colorectal polyps and are widely considered to be a good predictor of colon cancer. Down-regulation of apoptosis in epithelial cells can lead to ACF formation.

Bioactive compounds found in grapefruit, such as limonin and naringin, lower inducible Nitric Oxide Synthase (iNOS) in colon cells, an enzyme known to be overexpressed in colon cancers of humans and rats.<sup>7-9</sup> Excessive nitric oxide production by iNOS can reduce DNA repair enzymes and suppress apoptosis by nitrosylation of caspases.<sup>10,11</sup> Caspases (aka "executioner proteins") are proteases that play an essential role in apoptosis.

Additionally, limonin also lowers levels of Cyclooxygenase-2 (COX-2), an enzyme that is up-regulated in many types of cancers.<sup>7,12</sup> COX-2 is known to contribute to inflammation, abnormal cell proliferation, and reduced apoptosis.<sup>13</sup> Elevated levels of iNOS or COX-2 leads to a microenvironment that contributes to the proliferation, survival, and migration of tumors.<sup>14,15</sup>

In short:



www.nitisingical.com/colon\_cancer\_pictures.html

## APPLICATIONS/NUTRITION

There are various nutritional benefits found in grapefruit. It is necessary to evaluate the type of grapefruit and the nutritional components that are beneficial for health and cancer prevention. The type of grapefruit, natural or irradiated, is important when considering the effectiveness of the bioactive compounds. While irradiated grapefruit has been shown to decrease the ACF, natural grapefruit and isolated limonin were proven to be more effective. Grapefruit prevents the development of colon cancer and reduces the risk of reoccurrence by decreasing COX-2 and iNOS in rat colons that have been injected with AOM. Limonin and naringin are two of the primary bioactive compounds in grapefruit that decrease the development and proliferation of cancerous cells in the colon. Including grapefruit into a healthy diet will decrease the risk of developing colon cancer.

Not only does grapefruit provide anticarcinogenic compounds and phytochemicals, they also contain no fat, sodium, or cholesterol and are very high in vitamin C, vitamin A, fiber, and potassium. Other health benefits include: decreased digestive acidity, decreased atherosclerosis, and decreased risk for breast cancer and diabetes, increased immune system and weight loss.<sup>16</sup>

Before incorporating grapefruit into your everyday diet or increasing your average consumption, check with a physician or pharmacist if you are taking any medications. Grapefruit juice can interfere with the metabolism of certain prescription drugs and can result in a build up of the drug causing potentially serious side effects.<sup>17</sup>

## CONCLUSIONS

- Experimental diets resulted in lower iNOS and COX-2 levels, decreased cell proliferation, and an increase in apoptosis of epithelial cells in colon crypts
- Irradiated grapefruit, natural grapefruit, limonin, and naringin can be effective agents in preventing the development of colon cancer
- Natural grapefruit and limonin provided the most beneficial effects to AOM-induced colon cancer in rats
- Grapefruit may prevent and suppress colon cancer and decrease risk of recurrence

## REFERENCES

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