

学位論文の要旨

論文題目 EFFECTS OF LEMON PEEL POWDER ON INTESTINAL BARRIER
AND INFLAMMATION

(広島県産レモン果皮粉末による腸管保護作用に関する研究)

氏名 NGUYEN THI THANH TINH

1. Introduction (Chapter 1)

Ulcerative colitis and Crohn's disease are two distinct forms of the inflammatory bowel diseases (IBDs) that are chronic idiopathic disorders causing inflammation of the intestinal tract. The intestinal mucosa has the dual purpose of providing a barrier to prevent bacteria and toxins in the intestines into the circulatory system, while simultaneously absorbing the nutritional components. The IBD arises possibly from an impaired epithelial barrier leading to an exacerbated immune response to the resident microflora. High consumption of plant-derived foods helps to maintain a good health status and reduce the risk of some life-threatening diseases. *Citrus limon* is the third most important citrus species. They are known to include phenolic compounds, vitamins, minerals, dietary fiber, essential oils, and carotenoids, all which are beneficial for our health. Lemon peel is a by-product of lemon juice and still contains bioactive substances such as dietary fibers and polyphenols. The previous researches from our laboratory demonstrated that supplemental dietary fibers and polyphenols reduced the intestinal barrier defect and inflammation. However, the information of effects of the lemon peel in IBDs is quite limited.

The purpose of this study to examine a beneficial effect of lemon peel powder and explore the underlying mechanisms using a murine model of experimental colitis. I especially focused on the intestinal regulation of epithelial barrier and immune response. In addition, I examined which bioactive substances were responsible for the effect of lemon peel powder.

2. Effect of lemon peel powder in the murine model of colitis (Chapter 2)

This experiment aimed to examine the effect of lemon peel powder on the intestinal barrier defect and inflammation in the murine model of experimental colitis. Mice fed the diets containing whole lemon powder at 2.5% and 5% (w/w) for 16 days. The experimental colitis was induced by oral administration of dextran sulfate sodium (DSS) from day 8 to 16 (for 9 days). The supplemental lemon peel powder, especially at 5%, reduced the experimental colitis in mice, indicated by restored body weight loss and reduced disease scores. Histological analysis also revealed that the lemon peel powder reduced the structural damage of colon.

The results suggested that the reduction of colitis by lemon peel powder was involved in the restored tight junction protein including occluding, claudin-3, and claudin-7. The lemon peel powder also suppressed the robust expression of pro-inflammatory cytokines such as interleukin (IL)-6 and chemokine C-X-C motif ligand-2 in the colon. Taken together, the lemon peel powder reduced the colitis possibly through the reduction of intestinal barrier and immune responses in mice.

3. Bioactive components responsible for the lemon peel-mediated reduction of colitis (Chapter 3)

The lemon peel powder is rich in dietary fibers and polyphenols, which are known to be beneficial for the intestinal health. Therefore, this experiment separated the lemon peel powder into two fractions, which are rich in the dietary fibers and polyphenols, respectively, by methanol (MetOH) extraction method. To examine

the bioactive components in the lemon peel powder, the DSS-induced colitis mice fed the dietary fiber-rich MetOH extraction residue and the polyphenol-rich the MetOH extract. The MetOH extraction residue rich in dietary fibers reduced the DSS-induced body weight loss and disease score in a manner similar to the whole lemon peel powder, indicating the reduction of colitis. The MetOH extraction residue as well as the whole lemon peel powder reduced the impaired tight junction barrier and up-regulation of inflammatory cytokine in the colon. Whereas, the MetOH extract rich in polyphenols did not show the substantial effects on these parameters. The supplemental whole peel powder and MetOH extraction residue increased the fecal short chain fatty acids including acetate and butyrate. Although the underlying mechanisms were not fully understood, it seems that the short chain fatty acids produced from colonic fermentation of dietary fibers in lemon peel powder are at least in part responsible for the regulation of colonic tight junction barrier and inflammatory response in the colon.

4. Overall conclusion (Chapter 4)

Accumulating evidences suggest that the intestinal health is closely associated with the dietary nutrition. Our findings demonstrated that the supplemental lemon peel powder could be a novel dietary approach against intestinal inflammation and the related disorders. Our results also show that the dietary fibers are responsible for the lemon peel-mediated reduction of the colitis. Although the underlying mechanisms were not fully understood, the short chain fatty acids produced from colonic fermentation of dietary fibers in lemon peel powder are at least in part responsible for the regulation of colonic tight junction barrier and inflammatory response in the colon. The efficacy of lemon peel powder in humans should be required in the further studies.