

Plenary 2: Functional Food

Bioactive factors and bowel disease

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Background – Increasingly, nature is being exploited as a rich resource for the targeted development of new treatment modalities for diseases and disorders affecting the gastrointestinal system. These naturally-sourced agents, known as bioactives, can be derived from a surprisingly broad range of sources, varying from mammalian and marine species through to insects, plants, fungi and even bacteria. The spectrum of gastrointestinal conditions these bioactive factors could potentially treat, or prevent, is equally diverse, encompassing ulcerative and inflammatory conditions affecting all regions of the alimentary system, from the mouth, oesophagus and stomach, through to the small intestine and colon. The development and implementation of rigorously-controlled animal model systems of gastrointestinal disease is greatly facilitating the pre-clinical development of newly-identified bioactive agents. In addition to determining indications of clinical efficacy, these experimental model systems have the further capacity to provide important mechanistic information on the likely mode of action of the bioactives *in vivo*.

Objective – Intestinal mucositis is a serious ulcerative condition that develops primarily in the upper small bowel of cancer patients undergoing chemotherapy or abdominal radiotherapy. The aetiology of the condition is a result of the inability of chemotherapy agents to discriminate between rapidly-dividing tumour cells and the normal, rapidly-dividing cells which line the intestine. Often, the severity of intestinal mucositis may be the factor that limits chemotherapy dose, and hence the likelihood of tumour ablation. We utilized a rat model of chemotherapy-induced mucositis to assess the potential efficacy of several newly-developed agents. These included: (1) the herbal extract, Iberogast; (2) an extract derived from grape seeds (GSE); (3) Emu Oil and (4) the bacterium, *Streptococcus thermophilus* (TH-4).

Design – Two rat models of intestinal mucositis were established to investigate the potential efficacy of the bioactive agents. Model 1 was induced in male Sprague Dawley rats by administration of the antimetabolite drug, methotrexate. Model 2 was induced in female Dark Agouti (DA) rats by administration of 5-Fluorouracil (5-FU). Use of the female DA rat enables further studies to be conducted in the breast cancer setting, since these rats will develop breast cancer following administration of a mammary adenocarcinoma cell suspension. In each model, the bioactive agents were gavaged daily (1 ml) for 5 days prior to chemotherapy, continuing until kill at days 2, 3 and 4 after chemotherapy. Analyses included essential metabolic parameters (body weight, food and water intake, urine and faecal output) and the non-invasive ¹³C-sucrose breath test. Biochemical analyses included intestinal sucrase and myeloperoxidase activity. Qualitative and quantitative histological analyses were conducted on specimens of proximal, mid and distal jejunum.

Outcomes – Iberogast partially protected the upper small intestine from chemotherapy damage, although the effect was lost in the more distal regions of the small intestine, presumably due to enzymatic degradation. Grape Seed Extract resulted in reduced inflammation in the upper small intestine as evidenced by a decrease in myeloperoxidase activity. Moreover, there were indications of residual GSE bioactivity in the distal ileum, as determined by improvements in villus and crypt integrity. *Streptococcus thermophilus* TH-4 almost normalized the ¹³C-sucrose breath test after chemotherapy and improved histological parameters of intestinal integrity, identifying TH-4 as a new probiotic species. Importantly, Emu Oil resulted in a highly significant reduction in acute intestinal inflammation, combined with a significant stimulation of mucosal regeneration after chemotherapy. This could represent a new mechanism of action for Emu Oil, the accelerated intestinal re-growth potentially representing the result of an increase in enterocyte proliferation.

Conclusion – Through disparate mechanisms, naturally-sourced bioactive agents and formulations are demonstrating therapeutic promise as dietary adjuncts to chemotherapy regimens. The capacity for these agents to target different regions of the intestine suggests indications for intestinal disorders beyond chemotherapy-induced mucositis. Although mechanistic studies are in their early stages, it is likely that mammalian-, bacterial- and plant-sourced bioactive agents could be developed further to provide a new therapeutic strategy to accompany conventional medical approaches for diseases and disorders of the small and large bowel.

References

1. KL Tooley, GS Howarth, GP Davidson and RN Butler. Oral ingestion of *Streptococcus thermophilus* diminishes severity of small intestinal mucositis in methotrexate treated rats. *Cancer Biol Therap.* 5(6): 593-600 (2006).
2. GS Howarth, KL Tooley, GP Davidson and RN Butler. A Non-Invasive Method for Detection of Mucositis Induced by Different Classes of Chemotherapy Drugs in the Rat. *Cancer Biol Therap.* 5(11): 1189-1195 (2006).