# THE USE OF PROBIOTICS IN INTESTINAL PROTECTION

**By**

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## ABSTRACT

While studies have suggested that gastrointestinal pathogenicity associated with conditions such as inflammatory bowel disease and chemotherapy induced mucositis can be improved by the use of probiotics, the mechanisms of probiotic protection are not clearly understood. Such knowledge is necessary to achieve maximum benefit from such forms of treatment. These investigations were undertaken to initially establish a non-invasive measure of intestinal barrier function and then to examine the protective effects of different yoghurts on conditions which causes loss of barrier function: chemotherapy induced mucositis; inflammatory bowel disease (IBD) patients; and athletes in training.

Different yoghurts acted on different regions of the intestine in an animal model of methotrexate-induced small bowel damage. Sheep milk yoghurt decreased the severity of proximal small intestinal damage and increased sucrase activity. Probiotic LA1 (*Lactobacillus johnsonii* strain LA1) yoghurt improved intestinal function by maintaining small intestinal permeability with the development of methotrexate-induced damage. These yoghurts may enhance mucosal recovery after damage.

IBD patients' intestinal permeability was found to mirror their disease activity and may assist in monitoring disease activity and direct interventions. Intestinal permeability in moderately trained recreational athletes was elevated to a level of severity seen in disease affected intestines. The number of athletes with elevated intestinal permeability increased with the length of training. Colonic microflora metabolism, measured by faecal short chain fatty acids (SCFA), was significantly increased in IBD patients and athletes compared to healthy controls. Probiotic LA1 yoghurt significantly decreased faecal SCFA in athletes and IBD patients. SCFA also increased the adhesion of probiotic bacteria, which may affect their colonisation. Probiotic induced intestinal functional changes may be related to SCFA levels.

The function of the small intestine can be compromised to different degrees after chemotherapy drugs, under physiological stress and in disease. Probiotics may improve compromised intestines through enhancing recovery of the intestinal mucosa and the barrier function.

**DECLARATION**

This thesis contains no material which has been accepted for the award of any other degree or diploma in any institution. To the best of my knowledge and belief, this thesis contains no material that had been previously published or written by another person, expect where due reference is made in the text.

I give consent to this copy of my thesis being available for photocopying and loan.

Emma Southcott

Date 6th May 2003

Signature E Southcott

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## ABBREVIATIONS

CD – Crohn's disease

$^{51}$Cr EDTA - $^{51}$Chromium ethylene diamine tetra acetic acid

CRP – C - reactive protein

ESR – Erythrocyte sedimentation rate

GALT – Gastrointestinal lymphoid tissue

HB – Harvey-Bradshaw

HR – Heart rate

$HR_t$ - Heart rate threshold

HRP – Horse radish peroxidase

IBD – Inflammatory bowel disease

IgA – Immunoglobulin A

IL - Interleukin

L - Lactulose

LAB – Lactic acid bacteria

LGG – *Lactobacillus rhamnosus* strain GG

LA1 – *Lactobacillus johnsonii* strain LA1

LPS - Lipopolysaccharide

L Shirota – *Lactobacillus paracasei* subspecies *paracasei* strain Shirota

M - Mannitol

MTX - Methotrexate

NSAIDs – Non steroidal anti-inflammatory drugs

PCDAI – Paediatric Crohn's disease activity index

PEG – Polyethylene glycol

PP – Peyer's patches

Rh - Rhamnose

RI – Refractive index

SCFA – Short chain fatty acids

TNF – Tumor necrosis factor

UC – Ulcerative colitis

YC-180 – mix of *Lactobacillus bulgaricus* and *Streptococcus thermophilus*

ZO – Zonula occludins

## AIMS OF THESIS

This thesis seeks to better understand small intestinal permeability and its role in barrier function testing in chemotherapy induced mucositis, IBD patients and athletes. It further aims to elucidate the interaction of probiotic organisms in both healthy and compromised intestines. It is hoped this work will increase the understanding of the physiological function of intestinal permeability in relation to the luminal milieu in order to design therapeutic approaches to diseases and conditions with altered permeability.

## HYPOTHESES

The hypotheses of this thesis are that:

1. Measurements of small intestinal permeability can detect abnormalities in barrier function induced by chemical damage, stress, and disease.

2. Probiotics will improve small intestinal permeability in animal models of intestinal damage and in patients with intestinal disease.

3. Probiotics will favourably modify the metabolic activity of the intestinal flora.

## RESEARCH PLAN

The first study involved developing a methodology and protocol for intestinal permeability testing in a methotrexate-induced damage rat model in order to investigate the integrity of the barrier function. Chapter Two investigated the effect of fasting versus feeding state in rats on performance of the permeability test. The influence of probiotics on intestinal barrier function was evaluated. Chapter Three examined the small bowel damage induced by methotrexate in rats and the effect of probiotic intervention of either *Lactobacillus johnsonii* strain LA1 or *Lactobacillus bulgaricus* (YC-180) on intestinal function.

The second study determined the usefulness of small intestinal permeability in the assessment of inflammatory bowel disease. Chapter Four aimed to assess intestinal permeability as a non-invasive marker of disease activity and disease extent in paediatric inflammatory bowel disease patients. Intestinal permeability was evaluated as a means of monitoring the response to therapy and predicting disease relapse. Chapter Five investigated changes in intestinal function after a probiotic *Lactobacillus johnsonii* strain LA1 supplemented diet in IBD patients and healthy subjects.

The third study (Chapter Six) investigated the effect of training and probiotics on the intestinal barrier function of athletes. Runners had their exercise performance, intestinal permeability and faecal SCFA tested prior to and after a training program. The influence of a probiotic yoghurt (LA1) and placebo yoghurt on exercise performance and barrier function over a four week exercise program was tested.

The fourth study (Chapter Seven) observed the adhesion to intestinal mucus by two probiotic strains; *Lactobacillus johnsonii* strain LA1 and *Lactobacillus bulgaricus* (YC-180). The adhesion of these strains was compared to two of the most researched probiotic strains: LGG and L Shirota. The adhesion was measured with increasing levels of tributyrin, the triglyceride of butyrate, to determine the effect of butyrate on the mucus adhesion of these strains.