Summary: The digestive system, or “gut,” is extremely important for proper immune health, as Gut-Associated Lymphoid Tissue (GALT) comprises a large part of the immune system. Studies using various \textit{in vitro} models (conducted by ProDigest BVBA in Ghent, Belgium), and a human clinical trial (conducted by NIS Labs in Klamath Falls, Oregon) help explain EpiCor fermentate’s beneficial effects on the digestive and immune systems. These studies demonstrate EpiCor’s ability to support gut health through a variety of mechanisms:

- EpiCor acted as a prebiotic, which helps explain part of its role as an immune system strengthener.

- Laboratory models of the human digestive system show that EpiCor significantly increases the levels of butyrate, a short chain fatty acid (SCFA) associated with benefits for the gut and immune health. The models also demonstrated that EpiCor increased the levels of beneficial bacteria in the gut ecosystem.

- Previous studies show that levels of secretory IgA are significantly increased with EpiCor versus placebo in human clinical trials. This important antibody is associated with mucosal membranes and is vital to the body’s first line of defense against pathogens.

- In a flow-through model of the gut, EpiCor altered both the luminal population of bacteria and the population bound to the modeled gut wall.

- In both laboratory models EpiCor reduced the levels of pro-inflammatory cytokines.

- Finally, using the skin of the arm as a model of the gut lining, EpiCor reduced histamine-induced inflammation.
**Introduction**

EpiCor yeast fermentate has been shown in multiple published studies to support both the innate and adaptive parts of the immune system.\(^5\)\(^,\)\(^6\)\(^,\)\(^7\)\(^,\)\(^8\)\(^,\)\(^9\) Due to the complex interactions between the immune system and the digestive system (GALT), it seemed very likely that EpiCor would positively affect gut health. As a first step, EpiCor was studied in an *in vitro* prebiotic screening model developed by the University of Ghent and conducted by its related research company, ProDigest in Belgium.

**Figure 1. Simulator of the Human Intestinal Microbial Ecosystem (SHIME\(^®\))**

The first vessel represents the stomach/duodenum, the second the jejunum/ileum and the third through fifth the colon (ascending, transverse and descending respectively). *Photo © Toon Coussement courtesy of ProDigest.*

The model studied was the SHIME (Simulator of the Human Intestinal Microbial Ecosystem - Figure 1), using an established human gut flora inoculum. The system is designed to screen products for prebiotic and probiotic activity. To test for prebiotic effects, the relative amounts of SCFA levels and changes in populations of bifidobacteria and lactobacilli were measured. During this trial, cellulose was used as a negative control, and fructooligosaccharide (FOS) and inulin were used as positive controls.

**Definitions**

**Probiotic:** A probiotic is a live microorganism, which when administered in adequate amounts confer a health benefit on the host.\(^10\)

**Prebiotic:** A prebiotic is a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health.\(^11\)

**Synbiotic:** The term synbiotic is used when a product contains both probiotics and prebiotics.\(^12\)

**Effect of EpiCor on Short Chain Fatty Acids in the Model System**

EpiCor caused a similar increase in total SCFA as inulin and FOS in the study, moreover, it shifted the pattern of SCFA to produce more butyrate (significant in the comparison of EpiCor to FOS, \(p=<0.05\))\(^1\) as shown in the table below. This is very important because butyrate is thought to positively interact with the immune system in a variety of ways (see discussion section below for more information on the benefits of butyrate).
Table 1. The effect of EpiCor on SCFA

<table>
<thead>
<tr>
<th></th>
<th>EpiCor</th>
<th>Inulin</th>
<th>FOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetate (%)</td>
<td>48</td>
<td>57</td>
<td>64</td>
</tr>
<tr>
<td>Propionate (%)</td>
<td>30</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Butyrate (%)</td>
<td>21</td>
<td>14</td>
<td>9</td>
</tr>
</tbody>
</table>

**Effect of EpiCor on Bacterial Populations in the Model System**

The study results are reflected in the following graph (Figure 2), which shows the ability of EpiCor to increase the levels of the beneficial bifidobacteria and lactobacilli bacterial groups as compared to the cellulose control. These results suggest EpiCor acts as a prebiotic, with effects comparable to inulin and FOS. These additional gut health benefits, combined with data from other studies performed with EpiCor⁷,⁸ may further explain how EpiCor helps the body achieve immune balance.

![Graph showing the effect of EpiCor on SCFA](Image)

**Figure 2. The Effect of EpiCor on Bacterial Populations in the Model System**

Further experiments with ProDigest utilized the HMI Module (Host-Microbiota Interaction).² This is a flowing system, where the microbiota is passed over a layer of cells simulating the gut cell wall. This demonstrated that EpiCor not only modified the total gut flora (as shown in the SHIME model), but also modified which bacteria adhere to the simulated gastric wall. It showed a trend for increased adherence of Lactobacilli species, and a trend for decreased adherence of Clostridia species.

The EpiCor modified gut bacterial populations from both the SHIME and HMI experiments were further tested in a model to simulate the inflammatory response in the layer of cells simulating the gut wall. In both cases, the EpiCor-modified microbiota exerted a strong anti-inflammatory effect.

**EpiCor In Vitro and In Vivo Results Suggests Anti-Inflammatory Responses in the Gut³**

Previous research on animals has demonstrated the anti-inflammatory effects of EpiCor,¹³ which led to further studies on its anti-inflammatory benefits. A human clinical study was carried out using the epidermis of the human arm to simulate the gut lining.³

Each arm of 12 participants was scratched and then histamine added. The skin irritation combined with the histamine caused inflammation, and the inflammatory response was monitored by the initial increase of sub-cutaneous blood flow, followed by the subsequent decrease of flow as it returned to the baseline level.

Both the time taken to reach the maximum response in terms of blood flow (Tmax) and the time taken for the increased blood flow to return to baseline (measured as the slope of the decrease in blood flow) are relevant to the inflammatory response, and the return to baseline is termed...
the resolution of the inflammatory response. In each subject one arm was the “control” (a drop of saline solution was added one minute after the histamine) and the other was the “treatment” (a drop of an EpiCor extract in saline solution was added one minute after the histamine).

Clinical results demonstrated significantly reduced microvascular inflammatory responses to histamine-induced skin inflammation, and significantly reduced subjective scores of irritation at the inflamed sites treated with EpiCor compared with the sites treated with placebo (P < .05). The arm with the added EpiCor extract showed a faster resolution of the inflammation – the peak blood flow was reached in 7 minutes rather than 9 minutes, and the recovery to the baseline level was faster. (See Figures 3 and 4). In both cases the difference was statistically significant (p=0.05).

![Figure 3: Tmax](image)

**Discussion**

SCFAs produced by bacteria during digestion have been recognized for many years as sources of energy for the host, which are mainly derived from fermentation reactions in the distal sections of the digestive system. Recently, there has been considerable interest in the effects of SCFAs on immune health, in particular butyrate. Apart from butyrate’s association with energy, it is thought to interact directly with parts of the immune and digestive systems. Research has shown butyrate’s beneficial effects on the structure of the gut wall and on its ability to alter cytokine profiles in such a way that the immune response is modulated. The effects include increasing levels of IL-10, an anti-inflammatory cytokine.

Lactobacilli and bifidobacteria are both considered beneficial bacteria in digestion, and indeed, many probiotics contain these species. These species have been shown to help “exclude” pathogenic bacteria, thus reducing the possibility of disease, especially traveler’s diarrhea. They help balance the overall microbiota of the gut, leading to better and more regular digestion. Having the appropriate levels of the right bacterial species in the gut is also important for overall immune health. The combination of the potential prebiotic effects shown in the laboratory models and the increase in secretory IgA shown in human clinical studies strongly suggest that daily consumption of EpiCor may help balance the gut flora and beneficially modulate immune health.

Finally, a human clinical study model supported the in vitro studies that demonstrated anti-inflammatory effects. Inflammation in the gut is a normal immune response, but long term and sub-clinical inflammation can cause both transient and chronic damage to the individual. These studies show that EpiCor has the potential to modulate such responses.
References


