



EpiCor® Prevents And Reduces Inflammation In Two Separate Experimental Immune Animal Models



Summary: Two well-established animal models for inflammation were used to determine what beneficial effects EpiCor yeast fermentate may have on inflammatory conditions. These two trials, published as one scientific report in Evidence-Based Complementary and Alternative Medicine, demonstrate that EpiCor favorably impacts multiple acute and potentially chronic immunologic inflammatory control mechanisms. Results of the studies show:

1. **Inflammation Prevention/Reduction Model: Significantly Reduced Paw Swelling and Prostaglandin E2 (PGE2).** Study one examined whether EpiCor prevented or reduced inflammation. EpiCor significantly reduced ($p < 0.05$) paw swelling at all time points. Paw swelling and PGE2 levels were significantly reduced ($p < 0.05$) by approximately 50% and 25%, respectively.
2. **Inflammation Treatment Model: Significantly Reduced Arthritis Scores, anti-type II collagen and interferon-gamma levels (IFN- γ).** Study two examined EpiCor's ability to treat established inflammation (autoimmune arthritis model). EpiCor significantly reduced arthritis scores, antibody response to type II collagen, and IFN- γ levels were observed compared to controls (all parameters $p < 0.05$).



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Introduction

Diverse and significant benefits against cold/flu symptoms and seasonal allergies have been observed with EpiCor yeast fermentate in multiple published randomized trials.^{2,3,4} More studies were conducted to determine if EpiCor influences other immune conditions.

Researchers continue to study the relationship between nutrition, an unbalanced immune system and inflammatory diseases. Since inflammation can be affected through nutrition and EpiCor has been shown through *in vitro* studies to have anti-inflammatory properties,⁵ EpiCor was studied using two widely accepted animal models to examine EpiCor's role in modulating immune response to inflammatory substances. Carrageenan-induced paw swelling in rats and collagen-induced arthritis mouse models are two of the most commonly studied animal models for inflammation.⁶

In study one, carrageenan injection into the paws of rats is used as a model of localized inflammatory response, because it results in localized swelling and increased levels of circulating and tissue PGE2 and NGF.⁷

In study two, injection of type II collagen into mice is used as a model to produce an autoimmune response that resembles and provides an appropriate model for human arthritis.^{8,9}

The results of these studies show that EpiCor favorably impacts multiple acute and potentially chronic immunologic inflammatory control mechanisms.

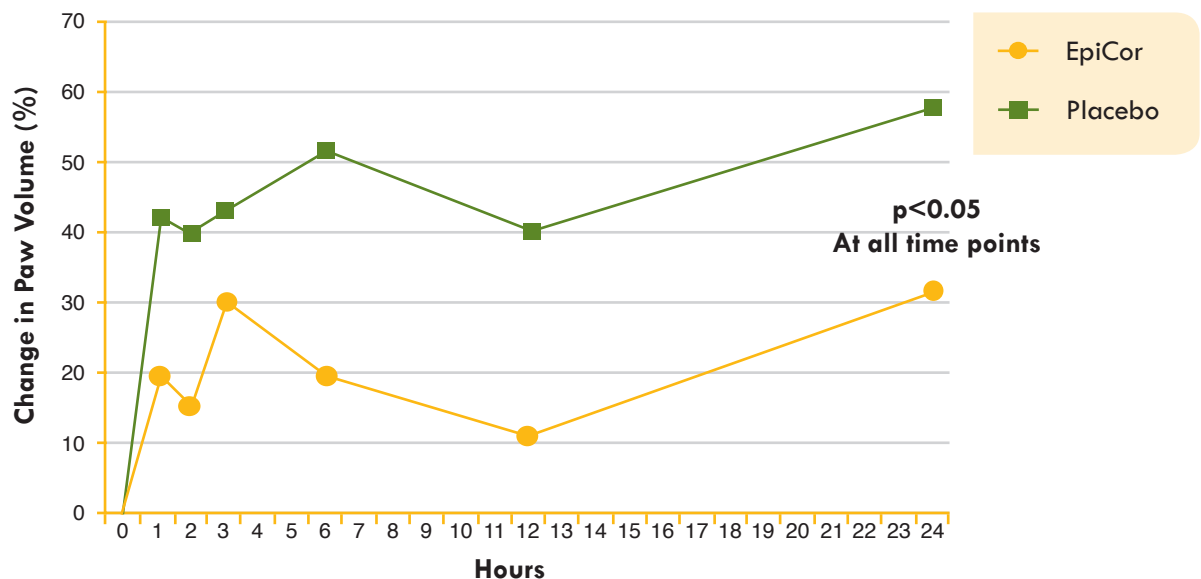
Study 1) Inflammation Prevention/Reduction Model

Study one examined whether EpiCor promoted anti-inflammatory effects in the carrageenan-induced edema model. For 14 days prior to carrageenan injection, rats were treated daily by gavage with EpiCor (7mg/kg body weight) or with the control only. All the rats were then injected with 1% carrageenan in one paw and saline in the other.

Significantly Reduced Paw Swelling

Rats that were pre-treatment with EpiCor resulted in reduced swelling of the carrageenan-injected paws at all times tested (1, 2, 3, 6, 12, and 24 hrs.) compared with swelling of paws in the control-treated rats ($p < 0.05$). At 24 hrs., the rats pre-treated with EpiCor showed a 50% reduction in paw swelling (Figure 1).

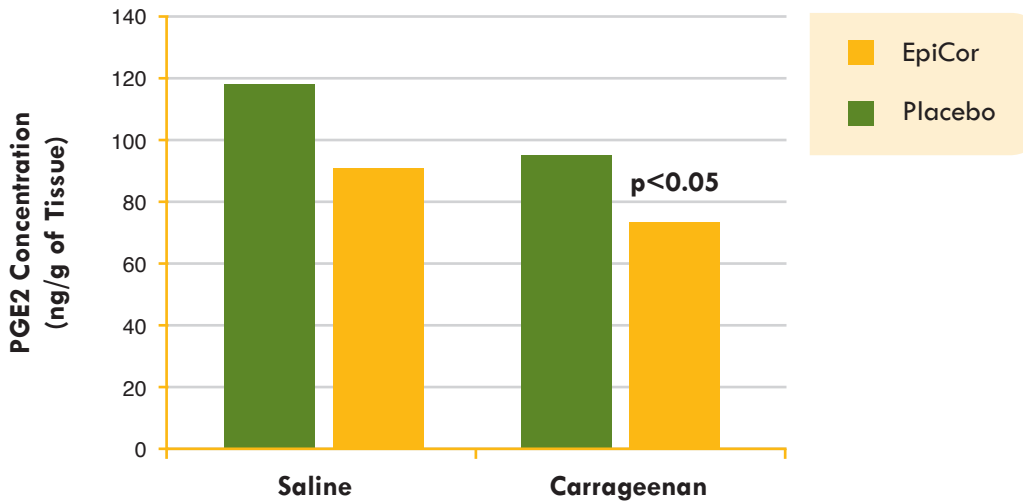
Figure 1. Reduced Swelling of Carrageenan-Injected Rat Paws Compared to Control Treated Rats



Significantly Reduced Levels of PGE2

One of the major mediators of localized inflammation in this model and in other inflammatory conditions is PGE2.^{10,11,12} Rats that were pre-treated with EpiCor saw a 25% reduction in PGE2 levels in their paws compared to the control, for both the saline and the carrageenan-injected paws (Figure 2). The reduction in PGE2 levels in the carrageenan-injected paws was statistically significant ($p < 0.05$). The control-treated rats saw a significant increase in NGF in response to carrageenan, while with EpiCor treated rats saw no significant increase in NGF in response to carrageenan.

Figure 2. PGE2 Levels in Paws of Rats Treated with EpiCor Compared to Control.



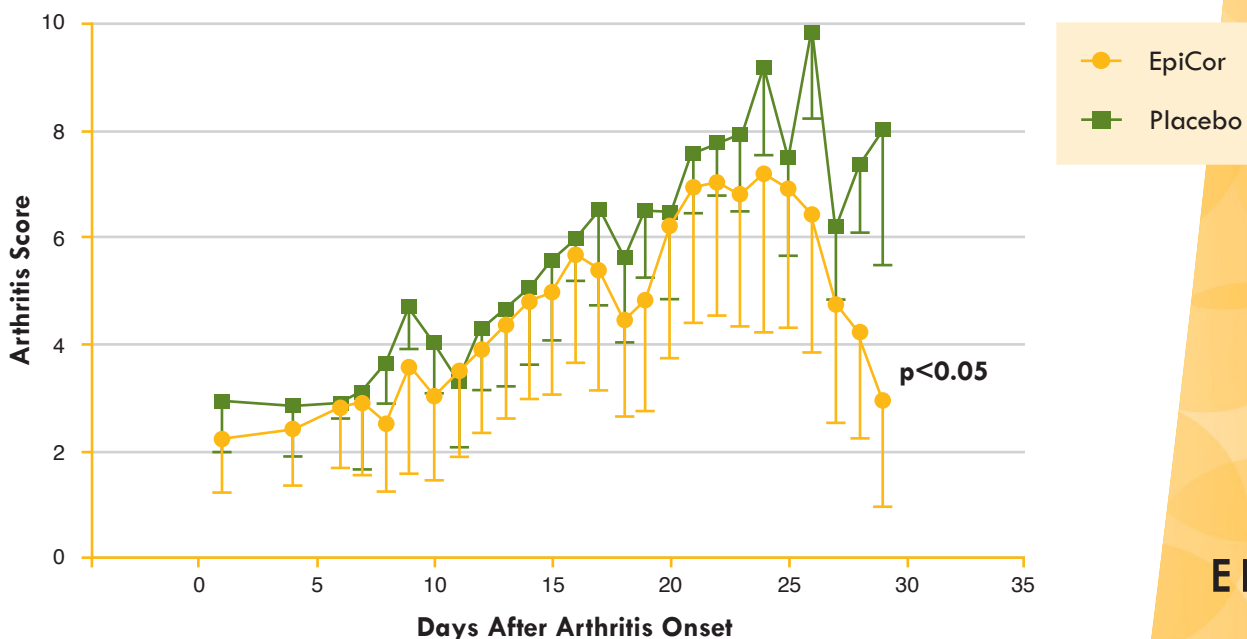
Study 2) Inflammation Treatment Model

Study two was a four-week trial that examined EpiCor's ability to treat established inflammation induced by type II collagen in mice (autoimmune arthritis model). After development of arthritis, mice were orally gavaged daily for four weeks with either EpiCor (7mg/kg body weight) or with the control only.

Significantly Reduced Arthritis Score

A decrease in the arthritis score was seen from day 18 to 29 in the EpiCor group (Figure 3). The study showed the mice receiving EpiCor had significantly lower arthritis scores at the end of the study ($p < 0.05$) compared to the control group.

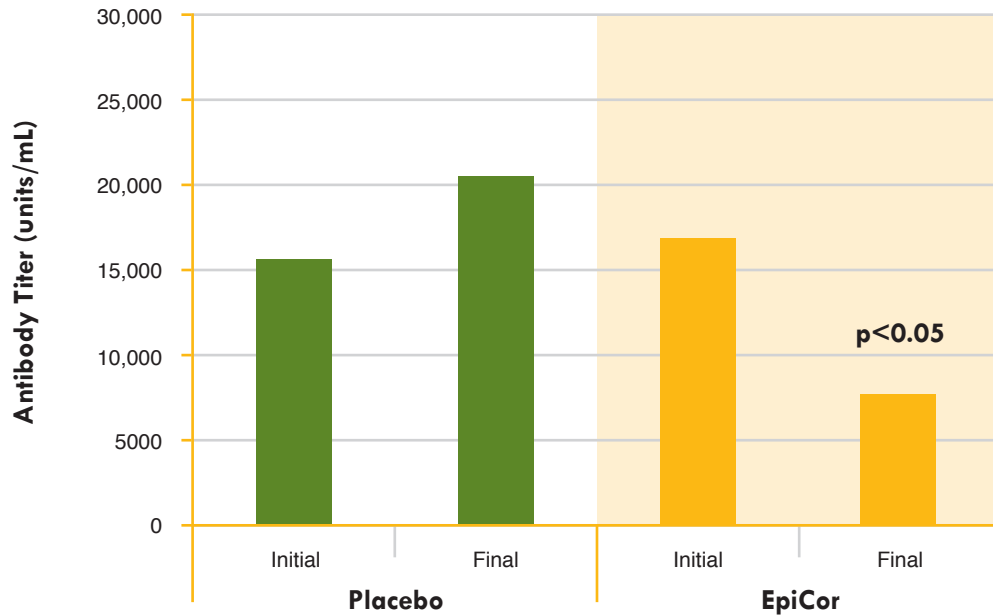
Figure 3. Effect of Treatment with EpiCor on Arthritis Development



Significantly reduced Anti-Type II Collagen Antibody Titers

EpiCor treated mice saw statistically significantly lower antibody response to type II collagen and antibody levels when compared to the mice in the control group at the end of the study (Figure 4).

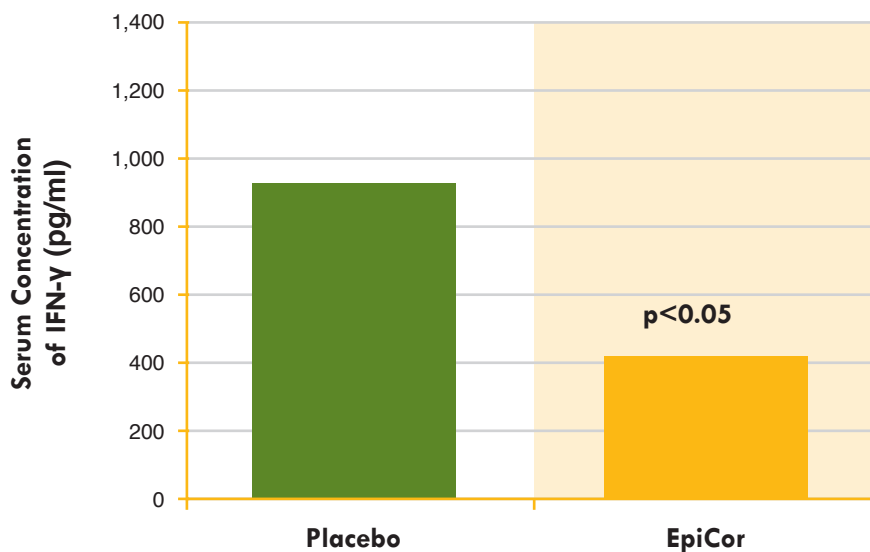
Figure 4. Anti-Type II Collagen Antibody Titers in Arthritic Mice Treated with EpiCor or with Control



Effect of EpiCor on IFN- γ levels in Arthritic Mice Treated with EpiCor and with Control

A statistically significant decrease ($p < 0.05$) was observed in IFN- γ levels in the EpiCor group when compared to mice treated with the control.

Figure 5. Effect of EpiCor on Serum Concentrations of IFN- γ



Discussions

The results of study one indicate that EpiCor reduces the inflammatory response to carrageenan. A major mediator of the localized inflammatory response in this model is the proinflammatory PGE2¹¹, which has a role in other medical conditions as well. For example, in autoimmune diseases such as rheumatoid arthritis, PGE2 has a proinflammatory function.¹⁰ Prostaglandins, including PGE2, are also produced in large amounts during allergen exposure,¹³ and some conventional medicines reduce PGE2 levels as part of their respective mechanisms of action.¹⁴ A significant reduction in nasal congestion from seasonal allergies found in a past clinical trial utilizing EpiCor can now be partially explained from the favorable impact on PGE2 in this study.⁴

It is also of interest that a traditional Chinese medicine (Guizhi-Tang or GZT) utilized to treat the common cold, pyrexia and influenza is thought to favorably impact several immune pathways including the fairly recent finding of a reduction in PGE2.¹⁵ This medicine also contains a plethora of diverse compounds.¹⁶ These observations may provide a partial explanation of the favorable effects of EpiCor in significantly reducing the duration and incidence of cold and flu symptoms in clinical trials of vaccinated and nonvaccinated individuals.^{2,3}

Study two assessed the effect of EpiCor on the clinical severity of collagen-induced arthritis. Collagen-induced arthritis is known to cause a rapid onset of arthritis with severe pain, swelling and erythema. Results showed statistically significantly lower arthritis scores in the EpiCor group compared to the control animals. These results are further confirmed by reduced anti-type II collagen antibody titers and reduced IFN- γ levels in the EpiCor group compared to the mice in the control group.

Significant reductions in anti-type II collagen antibody titers and IFN- γ concentrations are important observations. IFN- γ is one of the primary endogenous mediators of inflammation and immunity and has diverse roles, including macrophage activation, tissue remodeling, host defense, and even enhancement of autoimmunity. Classic autoimmune conditions such as inflammatory bowel disease, lupus, multiple sclerosis, psoriasis, and rheumatoid arthritis display large concentrations of activated macrophages at inflammatory sites. These macrophages are believed to enhance the production of cytokines such as IL-6 and TNF. Hence, IFN- γ has been considered an autoimmune disease promoting or proinflammatory cytokine, as also suggested from the collagen-induced arthritis model. However, the complexity and diversity of the immune system and EpiCor for that matter is greater than previously appreciated. IFN- γ is now thought to have both promoting and suppressive roles in autoimmunity. Regardless, the moderate but significant ability of EpiCor to suppress IFN- γ in this study suggests one favorable anti-inflammatory pathway, and perhaps any further suppression would not necessarily suggest an enhanced positive outcome without some negative consequences. This supports a selective action of EpiCor, dependent on the health of the mammal and the timing of the sampling. This can be related to clinical studies whereby EpiCor was clinically beneficial but without adverse events compared to a placebo.

Conclusions

The results of these studies demonstrate that EpiCor, at a weight-adjusted human dose of 500 mg/day, acts as an effective immune modulator in both models. The mechanisms-of-action behind these multiple acute and potentially chronic inflammatory control mechanisms, indicate possible benefits for humans.



Carried out by: KGK Synergize Inc., London, Ontario, Canada.

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