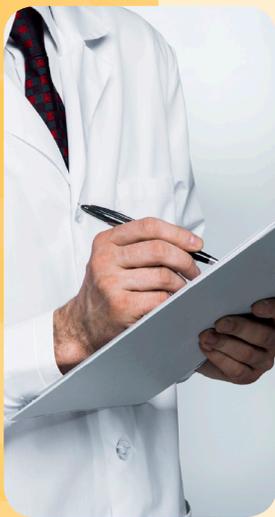




## The Importance of a Balanced Immune System

### Summary of Human Clinical Trials on EpiCor®

Summaries of studies published in peer-reviewed journals.<sup>1,2,3,4,5,6</sup>



**EpiCor fermentate has undergone seven human clinical trials, all of which have been published in peer-reviewed scientific journals and have used a standard dose of 500 mg per day. Five of the seven trials conform to the “gold standard” of clinical design in that they were randomized, double-blinded, placebo-controlled trials. Results show that EpiCor supports a strong, healthy immune system while it balances immune response; and significant measurable results can be seen in as little as two hours. The scientific evidence demonstrates:**

1. Supporting a Strong, Healthy Immune System by Significantly Increasing Secretory Immunoglobulin A (sIgA).<sup>1</sup>
2. Balancing and Strengthening Immune Response by Reducing Serum Immunoglobulin E (IgE) (relative to placebo) While Increasing sIgA.<sup>1</sup>
3. Flu-Vaccinated Subjects Saw Significantly Reduced Incidence and Duration of Symptoms from Upper Respiratory Tract Infections (URTI).<sup>2</sup>
4. Non-Vaccinated Subjects Saw Significantly Reduced Incidence of Symptoms from URIs.<sup>3</sup>
5. Significantly Reduced Allergy Symptoms.<sup>4</sup>
6. Rapid Response by Significantly Increasing Serum Antioxidant Protection and Natural Killer (NK) Cell Activity in Just Two Hours.<sup>5</sup> Significantly Reduced Allergy Symptoms.<sup>5</sup>
7. Reduced Inflammatory Response to Histamine-Induced Skin Inflammation, Suggesting Similar Effects May Happen Across Mucosal Membranes After Consumption.<sup>6</sup>



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*Scientific summary written for international product developers, industry experts, academia, and health care professionals. Not for distribution to consumers.*

## SUMMARY OF RESULTS:

- Human Clinical Trial 1: Supporting a Strong, Healthy Immune System by Significantly Increasing sIgA<sup>1</sup>:** The first published trial was the only trial that used an in-house, open-label model on 22 healthy subjects. The trial studied whether EpiCor provided immune support by increasing sIgA, an antibody that is integral in the body's first line of defense. Results showed that EpiCor supports immune strength by significantly ( $P < .05$ ) increasing sIgA relative to baseline.
- Human Clinical Trial 2: Balancing and Strengthening Immune Response by Reducing IgE (relative to placebo) While Increasing sIgA<sup>1</sup>:** The second published trial was a randomized, double-blinded, placebo-controlled trial on 25 healthy subjects ages 18-43. This five-week trial examined EpiCor's effect on sIgA and IgE, which are antibodies associated with pathogen defense and allergies respectively. Results showed that EpiCor balanced and strengthened immune response by reducing IgE (relative to placebo) while increasing sIgA.
- Human Clinical Trial 3: Flu-Vaccinated Subjects Saw Significantly Reduced Incidence and Duration of Symptoms from URTIs<sup>2</sup>:** The third trial, published in a MEDLINE-indexed journal, was a randomized, double-blinded, placebo-controlled, 90-day trial on 116 healthy subjects ages 18-76. The trial examined whether EpiCor had a beneficial effect on the incidence and duration of cold and flu symptoms for subjects who had received a flu vaccination. Results showed that EpiCor supports immune strength by significantly ( $P < .05$ ) reducing the incidence and duration of cold and flu symptoms.
- Human Clinical Trial 4: Non-Vaccinated Subjects Saw Significantly Reduced Incidence of Symptoms from URTIs<sup>3</sup>:** The fourth trial, published in a MEDLINE-indexed journal, was a randomized, double-blinded, placebo-controlled, 90-day trial on 116 healthy subjects ages 18-94. The trial examined whether EpiCor had a beneficial effect on the incidence of cold and flu symptoms on subjects that did not receive a flu vaccination. Results mirrored the third trial showing EpiCor supports immune strength by significantly ( $P < .05$ ) reducing the incidence of cold and flu symptoms.
- Human Clinical Trial 5: Significantly Reduced Allergy Symptoms<sup>4</sup>:** The fifth trial, published in a MEDLINE-indexed journal, was a randomized, double-blinded, placebo-controlled trial on 96 healthy subjects, ages 18-70, that had tested positive for allergies. The 90-day trial studied EpiCor's ability to reduce allergy symptoms. Results showed that EpiCor significantly ( $P < .05$ ) reduced the incidence of certain allergy symptoms – especially nasal congestion – while increasing sIgA levels, which are associated with immune defense.
- Human Clinical Trial 6: Rapid Response by Significantly Increasing Serum Antioxidant Protection and NK Cell Activity in Just Two Hours<sup>5</sup>:** The sixth trial, published in a MEDLINE-indexed journal, was a randomized, double-blinded, placebo-controlled trial on 12 healthy subjects ages 18-55. This trial examined how quickly EpiCor had an effect on the body's immune system. Results showed that EpiCor begins to support immune strength rapidly by significantly ( $P < .05$ ) increasing antioxidant protection and NK cell activation.

**Human Clinical Trial 7: Reduced Inflammatory Response to Histamine-Induced Skin Inflammation, Suggesting Similar Effects May Happen Across Mucosal Membranes After Consumption<sup>6</sup>:** The seventh trial, published in a MEDLINE-indexed journal, was a single blind, placebo-controlled, crossover study involving 12 healthy subjects ages 18-55. Clinical results demonstrated significantly reduced microvascular inflammatory responses to histamine-induced skin inflammation, and significantly ( $P < .05$ ) reduced subjective scores of irritation at the inflamed sites treated with EpiCor fermentate compared with the sites treated with placebo. The effects using a topical skin model suggest that similar events may happen when the EpiCor is introduced across mucosal membranes after consumption.



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# HUMAN CLINICAL TRIAL 1: Supporting a Strong, Healthy Immune System by Significantly Increasing sIgA

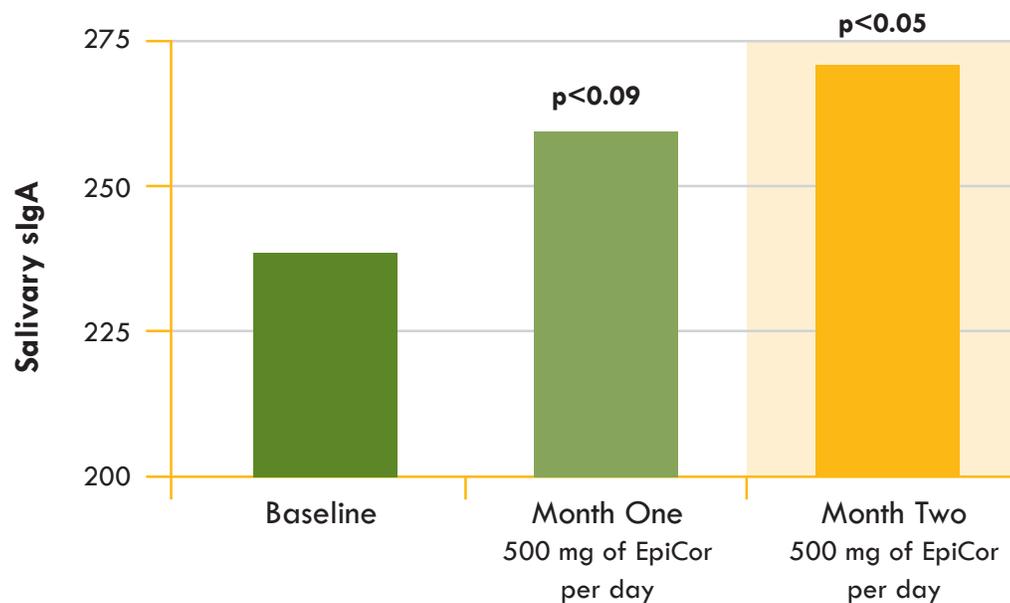
*A summary of a study published in the Open Nutrition Journal<sup>1</sup>*

sIgA is an antibody that is part of the human body's first line of defense and is integral to a healthy immune system. This antibody is produced from the mucosal-associated lymphoid tissue, which accounts for over 70% of the total immune system. As the majority of human infections arrive via breathing, touching and eating, sIgA is an essential part of the body's initial immune defense against pathogen exposure. Embria sponsored the first human clinical trial to establish whether EpiCor provides immune support by increasing beneficial salivary sIgA levels.

Twenty-two healthy subjects who had never taken EpiCor before, were recruited for this in-house, open-label 90-day trial. During the first 30 days of the trial, baseline concentrations for each subject were established for sIgA by measuring saliva samples, which were collected twice a day, three times a week. For the remaining 60 days, the subjects were then given one 500 mg capsule of EpiCor per day while researchers continued monitoring sIgA levels.

After 30 days, results showed a strong trend ( $p < 0.09$ ) for increased sIgA over baseline, and after 60 days the average sIgA levels among the subjects were statistically significantly higher ( $p < 0.05$ ) than the baseline levels (Figure 1). These results indicate EpiCor increased sIgA in just a matter of a few weeks. It also suggests that it takes time for the body to obtain the full benefits from EpiCor, and that continuous use is preferred for the most beneficial effects.

**Figure 1. The Effect of EpiCor on Salivary sIgA**



## HUMAN CLINICAL TRIAL 2: Balancing and Strengthening Immune Response by Reducing IgE (relative to placebo) While Increasing sIgA

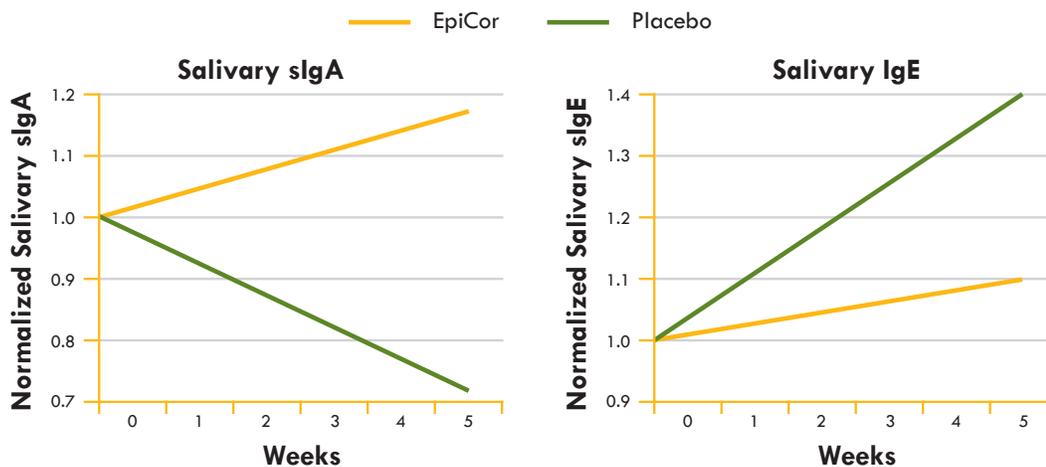
*A summary of a study published in the Open Nutrition Journal<sup>1</sup>*

Immune strength requires the immune system to respond appropriately to stressors that affect overall health. In human clinical trial one, EpiCor supported immune strength by increasing sIgA. Further studies were needed to show EpiCor's immune balancing abilities by simultaneously increasing sIgA and reducing unfavorable immune responses such as those represented by allergy symptoms. IgE is an antibody associated with the allergic reactions to harmless substances such as pollen and dust. IgE primes allergic response by binding to Fc receptors found on the surface of mast cells and basophils. The second human clinical trial investigated the effects of EpiCor on the immune markers, sIgA and IgE, as well as the incidence of allergy symptoms.

The trial used a double-blinded, placebo-controlled model on 25 healthy subjects, ages 18-43, and was conducted in the spring when allergies become an issue for some people. Subjects were given either EpiCor (500 mg) or placebo for five weeks.

At the end of the trial, subjects showed decreased IgE in the EpiCor group relative to placebo which suggests the important immune balancing effects of EpiCor. Specifically, IgE was expected to show an increase during the time frame of the trial because of its association with the onset of allergies. In the placebo group, results showed the expected increase in IgE while also showing a decrease in sIgA. However, the EpiCor group showed increased sIgA levels while IgE levels remained nearly at baseline (Figure 2). Laboratory results confirmed standardized questionnaire findings where subjects reported fewer allergy problems than usual. The questionnaire also showed that the EpiCor group reported significantly fewer health complaints compared to the placebo group.

**Figure 2. The Effect of EpiCor on Salivary sIgA and IgE**



It was also observed in this trial that cytokine profiles were modulated in the EpiCor group – again demonstrating the immune balancing properties of EpiCor. This result is consistent with EpiCor research using animal models that also demonstrated the multiple effects of EpiCor and its ability to support immune strength by helping to balance immune response and prevent over-reaction such as inflammation.

Although the results did not reach full statistical significance due to both the small number of subjects and the shortness of the trial, it showed a strong trends and led to larger more definitive human clinical trials.



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## HUMAN CLINICAL TRIAL 3: Flu-Vaccinated Subjects Saw Significantly Reduced Incidence and Duration of Symptoms from URTI

*A summary of a study published in Urological Nursing<sup>2</sup>*

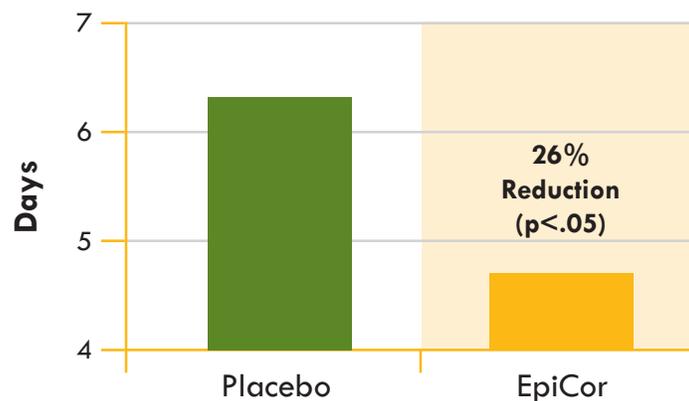
URTIs are reported to be the most commonly contracted illness. Maintaining a balanced, healthy immune system is expected to reduce the average number of days with URTI symptoms. The third human clinical examined whether EpiCor reduced the incidence and duration of cold and flu symptoms.

To determine the effect of EpiCor on strengthening the immune system, a 90-day trial was conducted in South Dakota during the worst expected cold and flu months – Jan. through Mar. The trial was a double-blinded, placebo-controlled trial on a group of 116 adults, ages 18-76, who had been vaccinated against the flu. This large group was chosen to represent the general vaccinated population.

At the beginning of the trial, subjects received physical examinations at screening to ensure a healthy study population and were randomly assigned to receive either EpiCor (500 mg) or placebo. Fasting blood samples were taken at randomization and at weeks six and twelve (when the trial ended). In addition, each subject was instructed to record the incidence, duration and severity of cold and flu symptoms.

The EpiCor group had statistically significantly reduced ( $p < 0.05$ ) incidence of URTI symptoms compared to the placebo group. Additionally, when the EpiCor group had URTIs, the duration of symptoms was significantly shorter. The average number of days with symptoms was significantly reduced by 26% (Figure 3).

**Figure 3. The Effect of EpiCor on the Number of Days with Symptoms Experienced by Vaccinated Subjects**



## HUMAN CLINICAL TRIAL 4: Non-Vaccinated Subjects Saw Significantly Reduced Incidence of Symptoms from URTIs

*Published in the Journal of Alternative Complementary Medicine<sup>3</sup>*

The fourth human clinical trial was a double-blind placebo-controlled trial on 116 healthy subjects, ages 18-94, who were not vaccinated against the flu. This trial was during the same time frame and place as the third trial – in South Dakota during the cold and flu season. Also, the same methodology and protocols were used. Because of this, results were expected to be very similar to and confirm the findings in the third trial. There was a significant reduction in the incidence of symptoms and a strong trend toward reduced duration of symptoms. As in the third trial, the average number of days with symptoms was reduced by 26%. These results along with the third trial results suggest that flu vaccination does not affect the efficacy of EpiCor.

# HUMAN CLINICAL TRIAL 5: Significantly Reduced Allergy Symptoms

*A summary of a study published in Advances in Therapy<sup>4</sup>*

Previously, in human clinical trial number two, EpiCor was shown to support immune strength and balance immune response by simultaneously helping increase sIgA while reducing IgE as compared to placebo. Animal studies also suggested EpiCor's ability to balance immune response by significantly reducing inflammation. These results from previous studies led to the fifth trial. This trial examined EpiCor's ability to balance immune response by helping reduce the incidence of certain symptoms from environmental allergens.

In this double-blinded, placebo-controlled trial, subjects had to test positive for a susceptibility to allergies. Ninety-six healthy subjects, ages 18-70, tested positive and were randomized to take EpiCor (500 mg) or a placebo. The 90-day trial took place in South Dakota during the 2008 spring allergy season.

The highest total pollen counts occurred during the first six weeks of the clinical trial. During this high pollen count period, the EpiCor group showed statistically significant reductions in several symptoms commonly associated with seasonal allergies. The EpiCor group had the greatest reductions in symptom incidence and severity when total pollen counts were highest, as would be expected. The largest symptomatic impact occurred with nasal congestion showing a 43% reduction in days with symptoms compared to placebo (Figure 4). The most significant symptom reductions were:

## Reduction in nasal symptoms

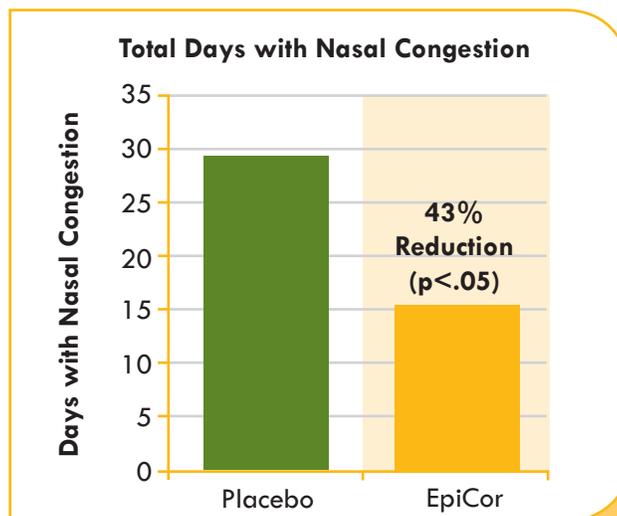
- Reduction mean severity ( $p=0.03$ )
- Runny nose ( $p=0.005$ )
- Nasal congestion ( $p=0.04$ )

## Trend toward reduction in itchiness and sneezing

Subjects were also asked to record when they used rescue medication for severe allergies. The EpiCor group used statistically significantly less rescue medication for allergies compared to the placebo group. Biochemical data mirrored the effectiveness observed in the allergy diary and questionnaire comparing EpiCor to Placebo:

- The number of selective allergy producing lymphocytes was reduced in the nasal smears ( $p<0.05$ )
- Downward trend of mean eosinophil percentage in nasal smears ( $p=0.056$ )
- Downward trend of mean serum basophil percentage ( $p=0.082$ ).

During the trial sIgA levels were measured for both groups. Subjects taking EpiCor had significantly increased levels of sIgA compared to placebo, which may play a role at mucosal protection. This study confirms previous studies suggesting that EpiCor helps strengthen and balance immune response without depressing the immune system.



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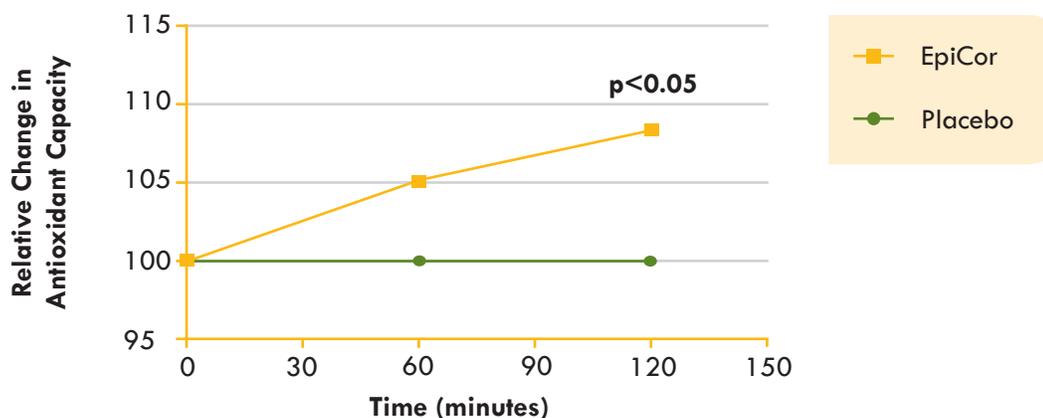
## HUMAN CLINICAL TRIAL 6: Rapid Response by Significantly Increasing Serum Antioxidant Protection and Natural Killer (NK) Cell Activity in Just Two Hours

*A summary of a study published in the Journal of Medical Food<sup>5</sup>*

Previous human clinicals tested the ability of EpiCor to support immune strength and balance immune response. The sixth human clinical trial studied how quickly EpiCor can benefit the immune system.

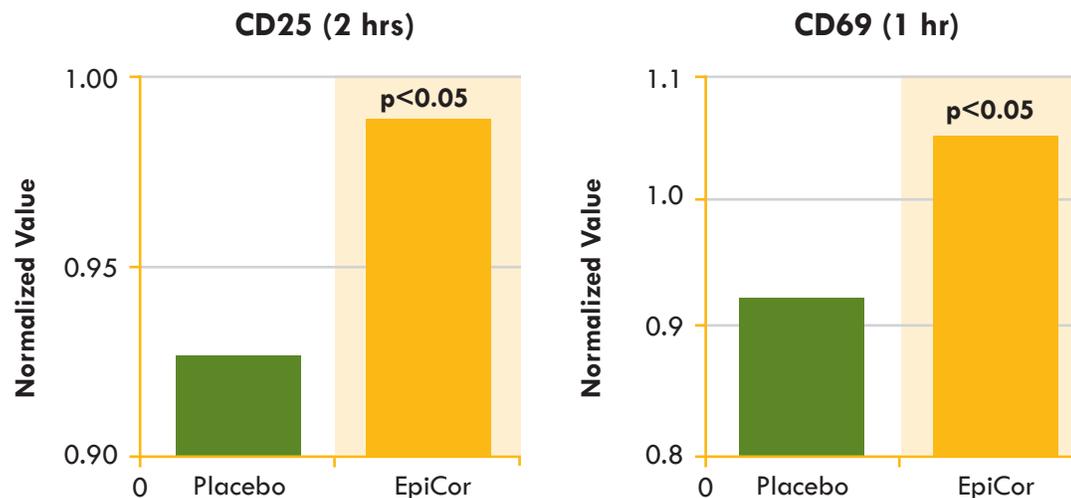
In this double-blinded, placebo-controlled trial 12 subjects, ages 18-55, were given either EpiCor (500 mg) or a placebo. The antioxidant protection capacity started rising very rapidly in the EpiCor group. After two hours the EpiCor group had statistically significantly higher serum antioxidant protection capacity than the placebo group (Figure 5).

**Figure 5. The Effect of EpiCor on serum antioxidant protection capacity**



Furthermore, this human clinical showed that NK cells were activated in the same time frame. Within two hours of ingesting 500 mg of EpiCor, both the CD25 and CD69 activation markers of serum NK cells were significantly increased (Figure 6).

**Figure 6. The Effect of EpiCor on NK Cell Activation**



These rapid responses complement the slower, modulatory effects of EpiCor, such as the increase in salivary sIgA and the ability to reduce the incidence of certain symptoms caused by environmental allergens.

# HUMAN CLINICAL TRIAL 7: Reduced Inflammatory Response to Histamine-Induced Skin Inflammation, Suggesting Similar Effects May Happen Across Digestive Mucosal Membranes After Consumption

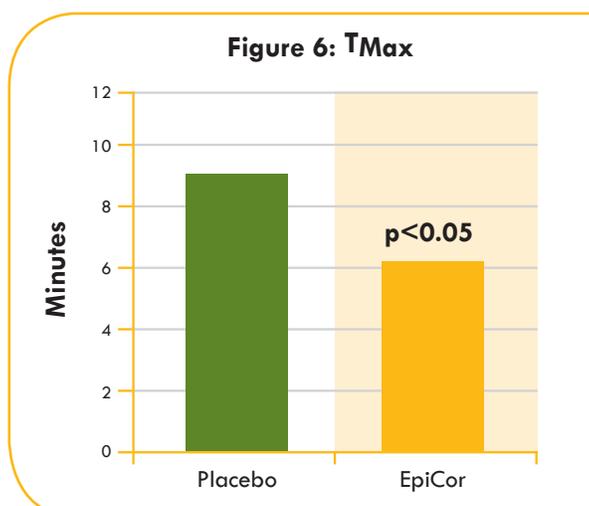
A summary of a study published in the *Journal of Medical Food*<sup>6</sup>

Inflammation is an important and necessary component of the innate immune system. Conversely, chronic inflammation, that is, inflammation that is not properly resolved and persists after the initial insult has been removed, can be harmful to the organism. The absence of inflammation resolution has been linked to a number of chronic diseases. The aim of this study was to expand the understanding of the anti-inflammatory properties of EpiCor by documenting specific effects on controlled inflammatory insults in vitro and in vivo.

A human clinical study was conducted using a single blind, placebo-controlled, crossover study involving 12 volunteers. All volunteers were in good health, and none of them were on antidepressant, diabetic, or allergy medications. The purpose of this procedure was to evaluate the resolution of a histamine-induced inflammatory response when the EpiCor solution was applied topically after the histamine response had been initiated.

The test procedure was performed in a manner similar to allergy skin testing with the exception of using the high sensitivity of the laser Doppler method to assess the microvascular blood perfusion, which allowed the use of much lower doses of histamine to provoke a measurable response.

On each healthy subject, a skin site was identified on the inner forearms where no major blood vessels were visible under the skin. Using the noninvasive laser Doppler probes, a baseline reading of the microvascular blood perfusion was performed and inflammation was induced on each skin site by applying a dilute solution of histamine and performing a scratch using a sterile lancet. After the histamine solution was removed EpiCor or placebo was applied to the site. After One (1) min, the EpiCor or placebo was removed and the laser Doppler probes were gently reapplied to the sites. After 10 minutes the probes were removed, and each subject was asked to score the level of itching on each skin site using a 100 mm Visual Analogue Scale. The procedure was simultaneously performed on left and right forearm, where the EpiCor solution was tested on one site and saline applied as a placebo control on the other site; study participants were unaware of which site received saline and which site received the EpiCor solution. The laser Doppler data were analyzed for the following parameters: the time to maximum blood perfusion (Tmax), and the slope of the curve generated during the resolution phase over time.



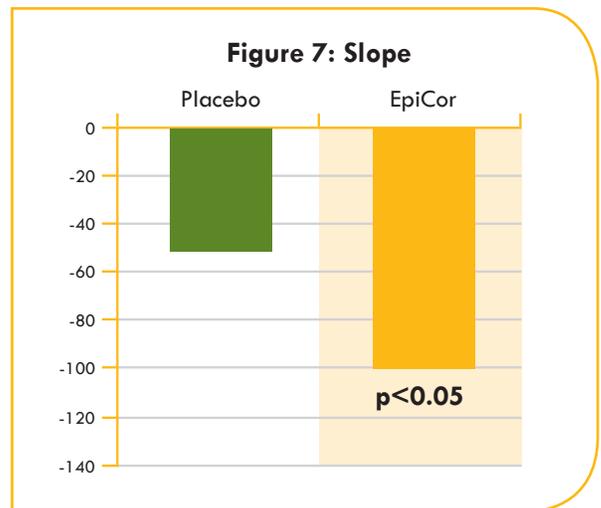
Results showed an accelerated resolution of the inflammatory insult in the EpiCor group. Among the 12 subjects, the observed average Tmax on the site treated with EpiCor was significantly shorter than the Tmax seen for the site treated with saline ( $P < .05$ ) (Figure 6). In addition, the slope of the curve after Tmax, during the resolution phase, was also significantly reduced in the EpiCor group compared with the saline-treated site ( $P < .05$ ) (Figure 7). This indicates that the increased blood perfusion caused by the histamine challenge resolved slower in the sites treated with saline, and that



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treatment of the inflamed site with the EpiCor resulted in faster inflammation resolution.

The results from the present work provide further clinical support for the anti-inflammatory properties of EpiCor. The data from the the skin model presented here may have broader relevance, for example, the effects may correlate with the effects of EpiCor consumption on the gut epithelium. This could indicate a promising role for the EpiCor fermentate consumption in protecting and maintaining a healthy gut environment through reduction of inflammatory reactions. For this exploratory study, a skin model was proposed for convenience, as events observed in the skin after topical application of the EpiCor fermentate likely can be extrapolated to events in the gut mucosa after the EpiCor fermentate is ingested.



## SUMMARY OF EPICOR EFFICACY SHOWN IN EPICOR CLINICAL TRIALS

The results from these seven human clinicals demonstrate the potential for EpiCor to play a beneficial role in helping healthy individuals maintain a strong, healthy immune response. EpiCor has been shown to have positive effects on key parts of the immune system that perform important functions against challenges. Embria's commitment to science ensures continued responsible research into EpiCor and its benefits.

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