MODE OF ACTION

Biochemical Markers Observed in Epicor® Studies

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EpiCor at 40x magnification.

A major portion of Embria's research on EpiCor has been with double-blind, placebo-controlled human trials, looking at clinical endpoints. These results were aimed at demonstrating statistically significant improvements of the consumer's health, and have been published in peer-reviewed Medline-indexed journals. Although reduction in symptoms of upper respiratory track infection (URTI) and allergies were the main thrust of the research, the importance of clinical biomarkers in demonstrating the causes of these beneficial effects was also recognized, and some of these results are reported below. All effects are *in vivo* and on healthy human adults unless otherwise stated.

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EMBRIA HEALTH SCIENCES IMMUNE HEALTH EXPERTS

Larry Robinson, Ph.D.
V.P. of Scientific Affairs
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Larry Robinson Ph.D., vice president of scientific affairs at Embria Health Sciences, is responsible for the ongoing research and scientific studies of existing products as well as the research and development of potential new products. He will ensure that all Embria products are backed by solid science, proven efficacious, and adhere to the strict quality standards that Embria is known for providing.

Dr. Robinson brings to Embria over 25 years of experience in the nutraceutical, pharmaceutical, and food ingredient industries. His background includes leading all phases of product R&D from planning through scale-up and commercialization. Previously, he was vice president of scientific affairs for Zila Nutraceuticals, Inc., where he led efforts developing Ester-E, and conducted all phases of research for Ester products. He also has expertise in microbiology, fermentation, enzymology, biotechnology, and business development. Larry's scientific background, combined with his experience in regulatory affairs, commercialization and marketing, make him ideally suited to lead Embria's technical efforts.

Dr. Robinson earned a bachelor's degree with double majors in biology and psychology, a master of science degree in microbiology with a minor in biochemistry from Auburn University, and a Ph.D. degree in microbiology from Rutgers University, followed by post-doctoral studies at the University of Minnesota. Dr. Robinson has been published extensively in nutritional, medical, biochemical and microbiological journals.

Stuart Reeves, Ph.D. ARCS
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Stuart Reeves, Ph.D., ARCS, is director of research and development, at Embria Health Sciences, LLC in Ankeny, Iowa, and is responsible for the company's internal research and external studies. He is author of The Key to a Healthy Immune System, and has been instrumental in spearheading research investigating the concept of balanced immune health. Dr. Reeves has authored dozens of peer-reviewed papers for such revered publications as the Journal of the Science of Food and Agriculture, Food and Agricultural Immunology, Advances in Therapy, Nutrition Research Journal, Journal of Alternative and Complementary Medicine, The Open Nutrition Journal and Urologic Nursing.

Dr. Reeves has extensive international experience in the food and beverage industries, including various aspects of processing and analysis. Most recently, he was the primary senior scientist for Diamond V Mills, Inc., Cedar Rapids, Iowa, and laid the scientific foundation for many of their research-based animal nutrition products.

Dr. Reeves earned a bachelor's degree in plant biology and chemistry from Imperial College, London, and a Ph.D. in plant biochemistry from Kings College, London, followed by post-doctoral studies at Cornell University. He subsequently held scientific positions in academia, government and industry, and published extensively in a variety of food related, agricultural and biochemical journals. Stuart currently serves as a board and panel member on various statewide and university committees in Iowa.

1. INNATE AND ADAPTIVE IMMUNE SYSTEM

- **Significantly increases Natural Killer (NK) Cell activation *in vivo* ([1]) and *in vitro* ([2])**
- **Significantly increases NK Cell activation in less than two hours post-consumption ([3])**

PHYSIOLOGY: NK cells are a type of white blood cell critical to the innate immune system. They provide a rapid immune response to virally infected cells as well as malignant cells. In many cases the NK cells will destroy the infected or malignant cell before the viral infection or malignant tumor can be established. Even if an infection becomes established, NK cells are also known to play a role in the slower acting but more specific adaptive immune response.

- **Significantly increases secretory salivary IgA (sIgA) versus placebo ([1,4])**

PHYSIOLOGY: sIgA is the main immunoglobulin (antibody) found in mucous secretions, including tears, saliva, colostrum and secretions from the genitourinary tract, gastrointestinal tract, prostate and respiratory epithelium. It is a major component of the body's defense against invading pathogens.

- **Serum IgG increased over the five-week consumption period in both groups, with the trend strongest in the EpiCor group ([1])**

PHYSIOLOGY: Serum IgG makes up about 75% of the antibodies found in blood. It is an important part of the immune system's ability to fight infections of body tissues. It binds many kinds of pathogens — including viruses, bacteria, and fungi — and protects the body against them using several immune mechanisms.

- **Increases B cell activation *in vitro* ([2])**

PHYSIOLOGY: B cells are an essential component of the human adaptive immune system. Their principal function is to make antibodies against antigens.

- **Significant increase in Interferon-gamma (IFN-y) ([3])**

PHYSIOLOGY: IFN-y is a cytokine that is critical for innate and adaptive immunity against viral and intracellular bacterial infections and for tumor control. IFN-y is now thought to have pleiotropic effects and thus can have both promoting and suppressive roles in autoimmunity.

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2. ALLERGY/ASTHMA

- **Strong trend toward reduction of eosinophils in EpiCor group versus placebo (4)**

PHYSIOLOGY: Blood levels of eosinophils are commonly elevated in people with asthma and other allergic diseases.

- **Significant decrease in lymphocytes in nasal smears in EpiCor group versus placebo ([4])**

PHYSIOLOGY: Increased lymphocytes would be expected in the nasal smears of allergy sufferers.

- **Trend toward relative decrease in serum IgE versus placebo ([1,4])**

PHYSIOLOGY: Pollen binds to IgE antibodies present on the mast cells of allergy sufferers. The mast cells, and similar cells like basophils activate to release chemicals, including histamine, into the blood vessels and tissues. The binding of histamine to histamine receptors produces the effects of inflammation to surrounding tissues and causes nerve stimulation, leading to symptoms of itchy, watery eyes, sneezing, runny nose, and itching of the nose and throat.

- **Significant decrease in PGE2 levels by 31% ([5])**

PHYSIOLOGY: Prostaglandins, including PGE2, are also produced in large amounts during allergen exposure, and some conventional medicines reduce PGE2 levels as part of their respective mechanisms of action.

- **Significant decrease in NGF by 22% ([5])**

PHYSIOLOGY: Excessive production of NGF was found in past studies of allergic rhinitis patients.

- **Trend toward lower serum basophil percentages ([4])**

PHYSIOLOGY: The mast cells, and similar cells like basophils activate to release chemicals, including histamine, into the blood vessels and tissues, which leads to allergy symptoms.

- **Dose dependent inhibition of LPS-induced nitric oxide (NO) with EpiCor, while positive control increased NO (in vitro bioassay) ([6])**

PHYSIOLOGY: In medicine, exhaled nitric oxide can be measured in a breath test to diagnose or monitor asthma or other conditions characterized by airway inflammation.

- **Total white blood cell count remained constant in the EpiCor group, whereas there was a mild trend towards an increase in white blood cells in the placebo group ([1])**

PHYSIOLOGY: While blood cells tend to proliferate in people due to the onset of seasonal allergies.

3. ANTIOXIDANT

- **Significant increase in serum antioxidant protection seen two hours post-consumption ([3])**

4. GUT HEALTH AND RELATIONSHIP BETWEEN GUT HEALTH AND IMMUNITY

- **EpiCor modulates the gut microflora, increasing the proportion bifidobacteria and lactobacilli (B&L)**

PHYSIOLOGY: B&L are lactic acid-producing bacteria constituting a major part of the intestinal microflora in humans and other mammals. The most important role of the microflora, from the point of view of the host, is probably to act in colonization resistance against exogenous, potentially pathogenic, microorganisms ([7]).

- **Increases production of butyrate**

PHYSIOLOGY: Butyrate is the major energy source for the intestinal epithelial cells, is considered to have anti-inflammatory effects, and has been studied for its role in nourishing the colonic mucosa and in the prevention of cancer of the colon ([8]).

- **Decreases production of proinflammatory cytokines**

PHYSIOLOGY: The change in composition of the microbial community of the gut caused a reduction in the production of inflammatory cytokines IL-8 and IL-1b in a model of the gut lining ([9]).

- **Individual IL-10 levels were increased after EpiCor consumption, while they remained unchanged in the placebo group ([1])**

PHYSIOLOGY: Knockout studies in mice suggested the function of this cytokine as an essential immunoregulator in the intestinal tract.

- **Significantly increases secretory salivary IgA (sIgA) versus placebo ([1,4])**

PHYSIOLOGY: In a healthy person, sIgA inhibits the colonization of pathogenic bacteria in the gut, as well as the mucosal penetration of pathogenic antigens. At least 80% of all the body's plasma cells, the source of sIgA, are located in the intestinal lamina propria throughout the length of the small intestine ([10]).

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5. INFLAMMATION

- **EpiCor treated mice had significantly lower arthritis scores versus placebo([5])**
- **Arthritic mice showed significant increase in IFN-γ levels in control mice versus mice fed EpiCor([5])**

PHYSIOLOGY: IFN-γ is one of the primary endogenous mediators of inflammation and immunity. IFN-γ has been considered an autoimmune disease promoting or pro-inflammatory cytokine, as also suggested from the collagen-induced arthritis model. IFN-γ is now thought to have pleiotropic effects and thus can have both promoting and suppressive roles in autoimmunity.

- **Arthritic mice showed significant increase in levels of immune complexes in control mice versus mice fed EpiCor.**

PHYSIOLOGY: Increased levels of immune complexes are associated with autoimmune diseases.

- **Significant decrease in NGF by 22% ([5])**

PHYSIOLOGY: Increases in NGF are associated with discomfort and pain with inflammatory responses because it impacts mast cells and afferent neurons. NGF is such a profound primary mediator of chronic pain that even vaccine research has been initiated in this area of medicine.

- **Rat paw edema severity and PGE2 levels were significantly reduced by approximately 50% and 31% respectively by consumption of EpiCor([5])**

PHYSIOLOGY: A major mediator of the localized inflammatory response in this model is the proinflammatory prostaglandin PGE2, which has a role in other medical conditions as well. For example, in autoimmune diseases such as rheumatoid arthritis, PGE2 has a pro-inflammatory function.

- **Individual IL-10 levels were increased after EpiCor consumption, while they remained unchanged in the placebo group ([1])**

PHYSIOLOGY: IL-10, also known as human cytokine synthesis inhibitory factor (CSIF), is an anti-inflammatory cytokine.

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