



## Preventive Medicine

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# A novel extract from bovine colostrum whey supports innate immune functions. II. Rapid changes in cellular immune function in humans

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## Abstract

### Objective

To evaluate acute effects of bovine colostrum low-molecular weight fraction (CLMWF) on selected aspects of innate immune function in healthy human subjects.

### Methodology

A placebo-controlled, double-blinded, randomized cross-over trial involving 12 healthy subjects, age 22–72, was conducted at NIS Labs during the year 2010. Placebo or 150mg CLMWF was given orally. Blood was drawn immediately before and at 1 and 2h after consumption.

### Results

A single dose of CLMWF, when compared to placebo, resulted in rapid increase in phagocytic activity of monocytes at 1h ( $P<0.12$ ) and polymorphonuclear cells at 1h ( $P<0.08$ ) and 2h ( $P<0.03$ ) after consumption. Observations included increased numbers of  $CD3^+$  T cells ( $P<0.05$ ), and a transient reduction in circulating  $CD3^-CD56^+$  natural killer (NK) cells at 1h ( $P<0.04$ ), returning to normal levels at 2h after consumption ( $P<0.96$ ). The relative increase of NK cells from 1 to 2h after consumption was not associated with an increase in CD69 or CD25 activation markers, suggesting that new NK cells were mobilized into circulation.

### Conclusion

The increased phagocytic activity and rapid transient changes in NK cell numbers suggest that upon consumption, interaction of CLMWF with immune cells in the gut mucosa triggers immediate events with systemic consequences.

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## Introduction

The immunomodulatory effects of colostrum from farm animals when consumed by humans have been demonstrated in a number of models, including infectious diseases (Lindbaek et al., 2006, Shin et al., 2005, Van Hooijdonk et al., 2000), exercise-induced immune suppression (Crooks et al., 2006, Shing et al., 2007), wound healing including gastrointestinal damage (Kim et al., 2005, Playford et al., 2000, Purup et al., 2007), and bone density (Du et al., 2011).

With the use of milk as a food on one side, and the development of novel drugs based on isolated colostrum compounds on the other side, the nutraceutical use of colostrum extracts in health management is an expanding niche (Séverin and Wenshui, 2005) and is receiving interest as complementary to or substitutes for vaccines and pharmaceutical drugs (Cesarone et al., 2007, Struff and Sprotte, 2007).

Research has been performed on whole colostrum and colostrum-whey at one end of the spectrum, and on separate compounds such as proline-rich polypeptide at the other end of the spectrum. However, no research has yet been done to document specific mechanisms of action of the simultaneous presentation of these compounds, such as those present in the fractionated colostrum extract CLMWF, to different components of the human immune system.

We have reported that a bovine immunoglobulin-depleted colostrum low-molecular weight fraction (CLMWF) has potent and rapid effects on the functional status of specific immune cells, and also leads to improved immune defense against bacterial and viral infections when consumed prior to infection (Benson et al., submitted as companion paper). This led to a need for a study of the effects in healthy humans, consuming CLMWF, allowing for evaluation of changes in immune status. Since this has its own circadian rhythm, and is highly affected by stress, a rigorous and well-controlled study design must be applied.

The immune system is unique in not being confined to a distinct organ or tissue. The defense of the body depends on ongoing immune surveillance, where many specialized immune cell types circulate the blood stream in alert but non-aggressive functional states, and are recruited into tissue when presented with specific signals on or from the endothelial blood vessel walls (Picker and Butcher, 1992). The recruitment process involves intricate interactions between receptors on the leukocytes and the endothelial cells, and leads to signaling events, such that the extravasated cells are in a different activation state (Crockett-Torabi, 1998, Po et al., 1995). Rapid changes can be induced by the central nerve system, and peripheral tissue control centers are important foci for decision making and input from the central nerve system (Bukovsky et al., 2009).

The mature immune cells divide their functions between innate immune defense reactions, and an adaptive immune activation that leads to immunological memory that sends educated cells to checkpoints in the body where they may most likely recognize a similar invading pathogen if it should reoccur. The innate immune response involves immediate recognition of foreign antigens and particles such as bacteria, and of the body's own cells if they have become transformed such as by viral infection or tumor development. The

recognition leads to killing by phagocytosis, secretion of signals that will attract more cells by migration, and also for some specialized cells such as monocytes and dendritic cells, the presentation of the ingested foreign components to the adaptive immune system.

NK cells represent cells that are immediately able to recognize and attack transformed cells, i.e. an organisms own cells that have become virally infected or undergone malignant transformation (Yoder and Litman, 2011). However, they do not perform these functions in the blood stream. They continually migrate between blood circulation and tissue as part of ongoing immune surveillance. They tend to accumulate in the blood stream under conditions of stress, where their ability to home into tissue becomes inhibited (Kimura et al., 2008, Schmid-Ott et al., 2009). This is one reason our study design and environment carefully took into account the reduction or elimination of stress factors. The process of extravasation and homing involves 1) initial margination of the cells as they roll on and attach to the endothelium, 2) migration through the endothelial layer, and 3) further migration through the extracellular matrix into tissue (Picker and Butcher, 1992). During all three phases the lymphocyte–endothelial interaction leads to cellular signaling events, changing resting circulating cells to active effector cells (González-Amaro and Sánchez-Madrid, 1999, Po et al., 1995).

Several nutritional products have been shown to support specific lymphocyte subset homing as part of normal immune surveillance (Jensen et al., 2000, Jensen et al., 2007, Jensen et al., 2011). The present study was undertaken to evaluate this fraction of bovine colostrum for its effects on the innate anti-viral immune system in vitro and in vivo. This paper builds directly onto the mode of actions as identified by cellular bioassays in vitro and verified in two animal studies (Benson et al., 2012), and shows data from a human clinical trial.

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## Section snippets

### Reagents and monoclonal antibodies

RPMI-1640, Histopaque 1119 and 1077, and phosphate-buffered saline (PBS) without calcium or magnesium were purchased from Sigma-Aldrich (St Louis, MO). Dulbecco's phosphate buffered saline was from Gibco (Invitrogen, Carlsbad, CA). Monoclonal antibodies directly conjugated with fluorochromes were purchased from Becton-Dickinson (San Jose, CA): CD3-PerCP, CD25-FITC, CD56-PE, and CD69-FITC. Carboxylated fluorescent beads were from Molecular Probes (Eugene, OR)...

### Colostrum and placebo

Bovine colostrum low-molecular...

### Increased phagocytic activity within 2h of consumption of single dose

The phagocytic activity of peripheral blood monocytes and PMN cells was evaluated ex vivo for each blood sample. On days where the study participants received placebo, the phagocytic activity of both cell types showed a reduction from baseline, indicating either a reduction during the morning hours, either as part of

the normal circadian rhythm or as a result of inactivity. On days where subjects received CLMWF, a rapid increase was seen for both cell types (Fig.2). The increased phagocytic...

## Significance of the results

This human clinical study has demonstrated that CLMWF had rapid and selective effects related to immune function. Two previous animal studies have shown that introduction of CLMWF across mucosal membranes (nasal and gastrointestinal) resulted in a faster and more efficient clearance of microbial pathogens [Benson et al., submitted as companion paper].

The rapid increase in phagocytic activity and lymphocyte trafficking points to the initiation of local events along the gut mucosa, resulting in...

## Conflict of interest statement

Dilip Patel is currently employed by the sponsor, Sterling Technology Inc. Neither Gitte S. Jensen nor Kathleen F. Benson has any conflict of interest or financial interest in the subject matter. The research was conducted at NIS Labs, which is an independent contract research laboratory...

## Acknowledgments

The authors are grateful to Steve G. Carter and Kimberlee A. Redman for excellent technical assistance. The testing for this study was performed at NIS Labs, Klamath Falls OR, which is an independent contract research laboratory specializing in natural products. The study was sponsored by Sterling Technology Inc., Brookings, South Dakota....

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2021, *Annals of Medicine and Surgery*

Citation Excerpt :

...In peritonitis, there is early activation of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin 1 (IL-1), and interferon gamma (IFN- $\gamma$ ), as well as recruitment of neutrophils followed by their replacement with macrophages [14–16]. The presence of bacterial infection on the peritoneal membrane also causes an immune response, including activation of macrophages that will phagocytose the bacteria [17]. Based on the immune-response mechanism, an alternative therapy could be the provision of additional immunomodulators [18]...

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## [Bovine colostrum enhances natural killer cell activity and immune response in a mouse model of influenza infection and mediates intestinal immunity through toll-like receptors 2 and 4](#)

2014, Nutrition Research

*Citation Excerpt :*

...Bovine colostrum supplementation in athletes has been reported to enhance performance, recovery, and body composition [10-14], although results have been mixed [15-19]. Some studies have suggested a reduction in symptoms of upper respiratory tract infections [20-22], whereas reports on nonspecific parameters of immune function, such as delayed type hypersensitivity, phagocytic activity, and altered numbers of circulating lymphocytes and subpopulations, in healthy nonimmune challenged subjects have been inconsistent [23,24]. The focus of our research has been to examine NK cell-mediated innate immune response during primary influenza infection and the effects of nutritional interventions....

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## [Functional benefits of ergothioneine and fruit- and vegetable-derived nutraceuticals: Overview of the supplemental issue contents](#)

2012, Preventive Medicine

*Citation Excerpt :*

...Benson, et al. (2012b) assess the ability of a novel extract from bovine colostrum whey to support anti-bacterial and anti-viral innate immune functions in vitro and in vivo and point out that the enhanced immune activity in vitro translates to improved microbial clearance in animal infection models. Following on this, Jensen, et al. (2012) discuss the rapid changes in cellular immune functions in humans due to the bovine Colostrum Low-Molecular Weight Fraction. The study was aimed at examining the relevant immune effects after consumption of a single dose of CLMWF in healthy humans....

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2012, Preventive Medicine

## [Diverse immune effects of bovine colostrum and benefits in human health and disease](#)

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