Effects of Echinaforce® treatment on the reactivity of ex vivo stimulated blood cells

Ritchie M. et al. Bute Medical School, University of St. Andrews, St. Andrews, Scotland, 2005 (unpublished)

1. Background

Echinaforce® is used to *strengthen the immune defence in case of susceptibility to cold infections*. Many factors can affect our immune defences and our susceptibility to infection like stress, malnutrition or recurrent infections. An immune modulator is meant to support the defence in case of susceptibility and to retard overreacting defences to minimize symptoms (Figure 1).

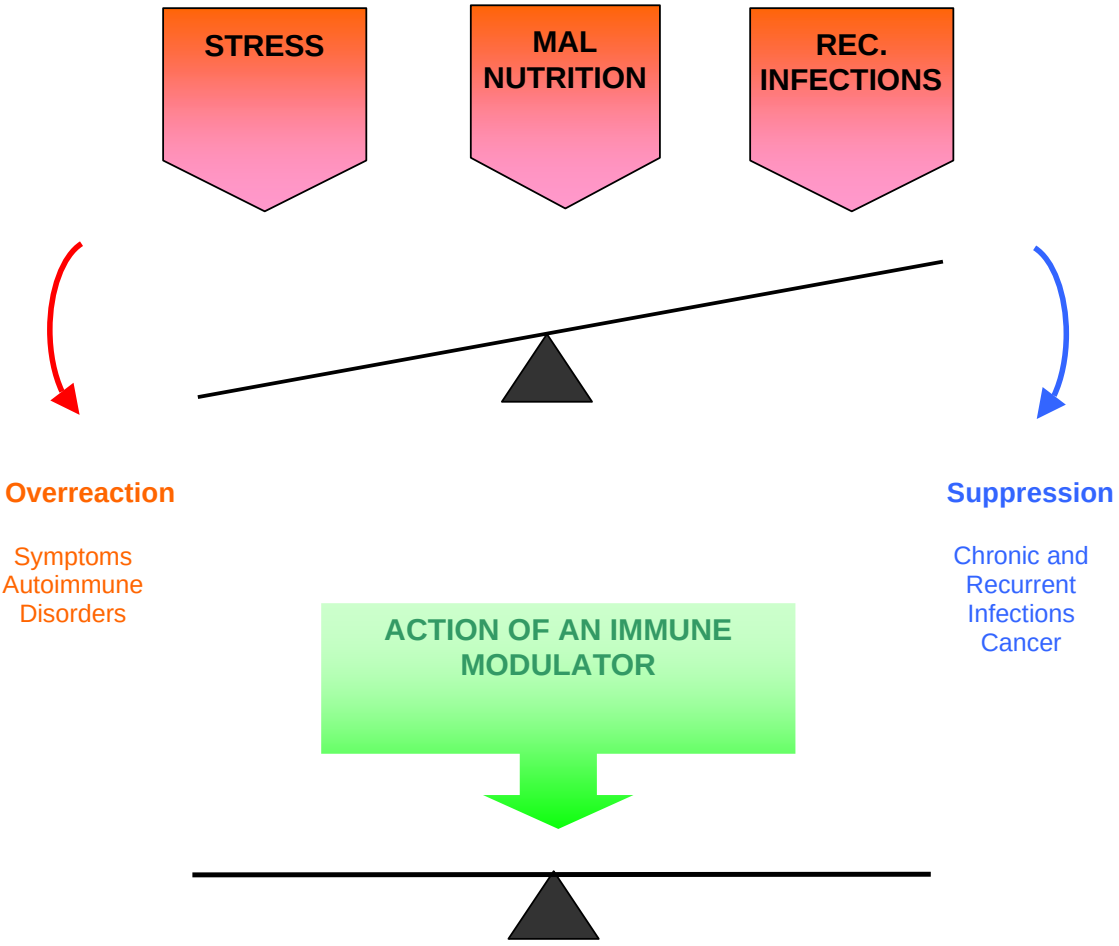

Figure 1: Our Immune system is a complex interplay of activating and inhibiting moments that in case of overemphasis can lead to **overreaction** or **suppression**. The role of an immune modulator is to **balance** this process via activating suppressed systems (susceptibility) and retarding overactive systems.

One option to balance the action of the immune system is to interfere with **soluble mediators**, which are produced by immune cells to communicate. These mediators constitute the “language” between the cells by which they fine-tune the outcome of an immune response. Each of these mediators has its specific role to either activate or inhibit above processes.

2. Question

Here we wanted to explore the effects of Echinaforce® on each of above mediators with known immunological function. First we investigated the generally valid, **overall effects** by Echinaforce® on all treated subjects. Secondly, we separated the subjects after weak / strong immune status and thus examined the **immune-modulatory** action of Echinaforce®.

3. Method

30 participants were included right after exposure to stress (examinations) and again under a stress-free period (5 weeks after examinations). Echinaforce® was applied to subjects at "low-dose" over 6 days and then was increased to "high-dose" treatment. The effects of Echinaforce® on mediators was determined after *ex vivo* stimulation and was expressed in comparison to baseline values before treatment (BL, Figure 2).

Figure 2: Illustration of the dosage regimen: "Low-dose" treatment started after recording of baseline values without medication. After 6 days the dosage was increased to 10 x 1 ml under "high dose" treatment.

4. Results

4.1 Overall Inhibition of Inflammation and Induction of Chemotaxis

In a first analysis all subjects treated with Echinaforce® were analyzed for generally valid principles of action. Typical inflammatory mediators like IL-1β or TNF-α were down-regulated whereas anti-inflammatory IL-10 was increased by Echinaforce®. Although the effects on single mediators were small, the overall picture displays a clear **anti-inflammatory action** by Echinaforce® through specific regulation of key-mediators in this process. Echinaforce® not only works on single mediators but rather in a **multi-levelled way**.

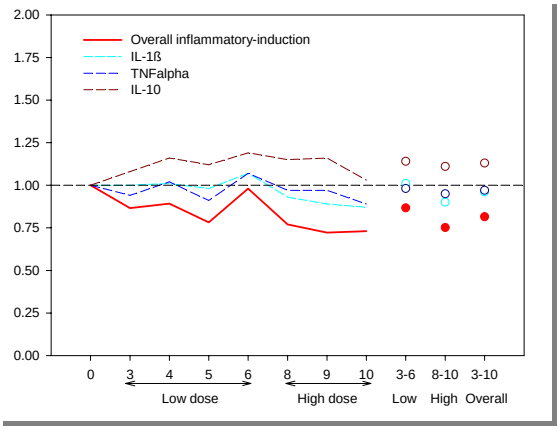

Figure 3: Intake of Echinaforce® and subsequent *ex vivo* stimulation results in an overall strong anti-inflammatory effect (**red curve**). Echinaforce® **reduces activators** and **supports inhibitors** of inflammatory processes in parallel.

Furthermore Echinaforce® mediated strong effects on chemokine-mediators MCP-1 and IL-8, which are released to attract immune cells to the site of an infection. As above, the effects of Echinaforce® on the single mediator were small, but taken similarly active mediators together, clinically relevant effects could be observed. **Interestingly, immunologically related mediators were affected by the drug in the same way.**

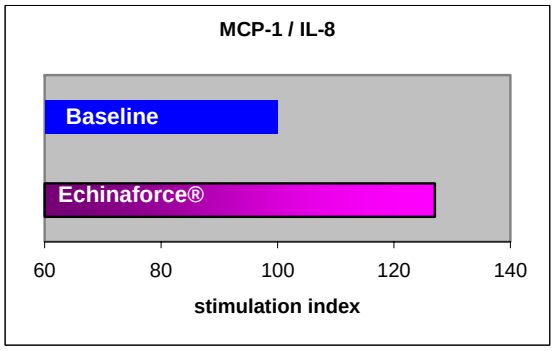

Figure 4: Echinaforce® potently induces chemokines IL-8 and MCP-1, which are important in recruitment of immune cells to the site of infection.

Echinaforce® lowers the inflammation and supports the production of chemokines in the overall population.

4.1 Adaptive Immune-modulatory Effects by Echinaforce®

A typical immune-modulator is thought to exert pharmacological effects under specific physiological conditions and where it is appropriate (Figure 1). In order to detect these **adaptive** actions, subjects were classified according to immunological conditions.
By doing so, many mediators were regulated individually and very specifically:

a) Acute-Phase-Proteins in low [Cortisol]

Cortisol is a very potent endogenous anti-inflammator that has been shown to reduce expression of acute phase proteins like IL-1β, IL-6, TNF-α and of IL-12. By reducing **responsiveness** of epithelial cells and viral docking receptors (**ICAM-1**), cortisol reduces infections. Echinaforce® in subjects with low cortisol levels (high responsiveness) lowered the production of IL-1 β, IL-6, TNF-α and IL-12 specifically. We therefore conclude that Echinaforce® in persons with higher responsiveness (due to low cortisol) lowers directly the expression of inflammatory mediators like acute phase proteins.

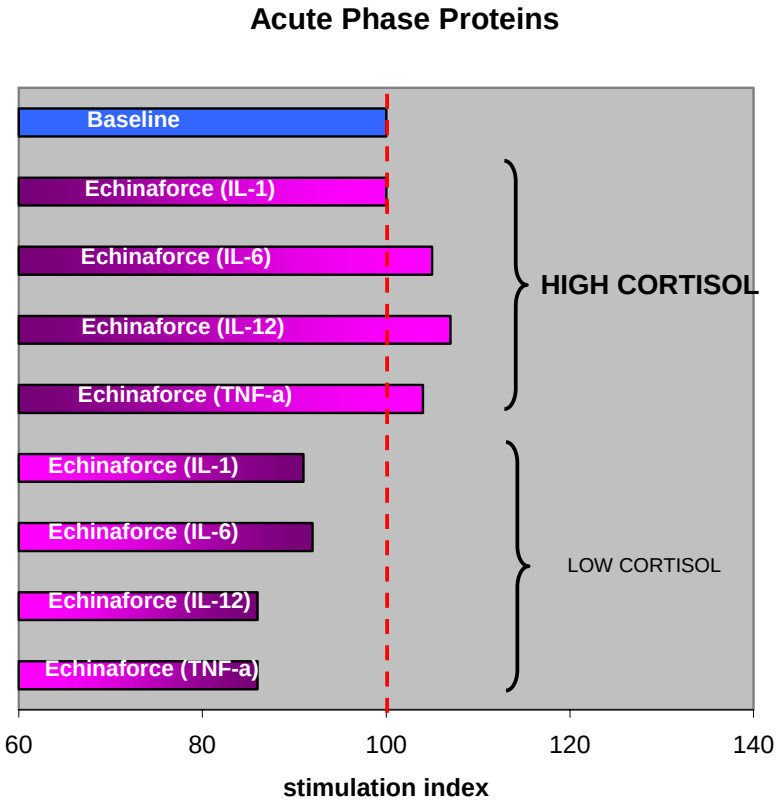

Figure 5: Effects on Acute-Phase-Proteins that are released immediately after viral infection and which are directly controlled by cortisol. Echinaforce® balanced these mediators in case of low-cortisol.

Echinaforce® specifically lowers inflammators in case of low endogenous cortisol (higher responsiveness) and therefore replaces the action of the latter in case of shortage.

b) IFN-γ during high-stress periods is induced

Echinaforce® activates Interferon-gamma (IFN-γ) in those who perceived stress over a period of time. Also IFN-γ was induced in susceptibles to cold infections. IFN-γ is a strong activator to defend against viral infections (**T_H1 response**).

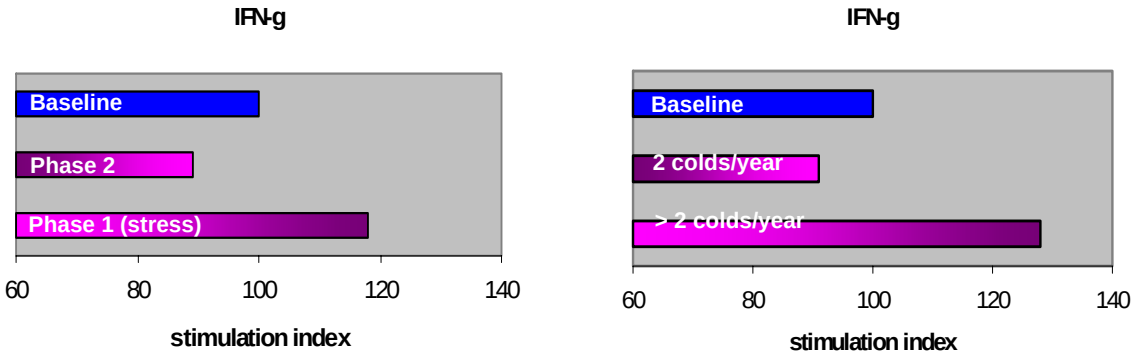

Figure 4 : INF-γ is a strong inducer of **anti-viral defence** and is induced by Echinaforce during stress-full periods and in case of susceptibility against cold infections.

Echinaforce® supports anti-viral defences during periods of stress and in case of susceptibility to cold infections.

c) Echinaforce® acts on low-/high Mediator production

A direct measure of the immunological capacity is the absolute level of mediators, which are produced after *ex vivo* stimulation (before treatment). IFN-γ, IL-8, IL-10 and MCP-1 in those with a low production rate are supported by Echinaforce® treatment. Echinaforce® therefore clearly displays supportive effects in those with low immune response.

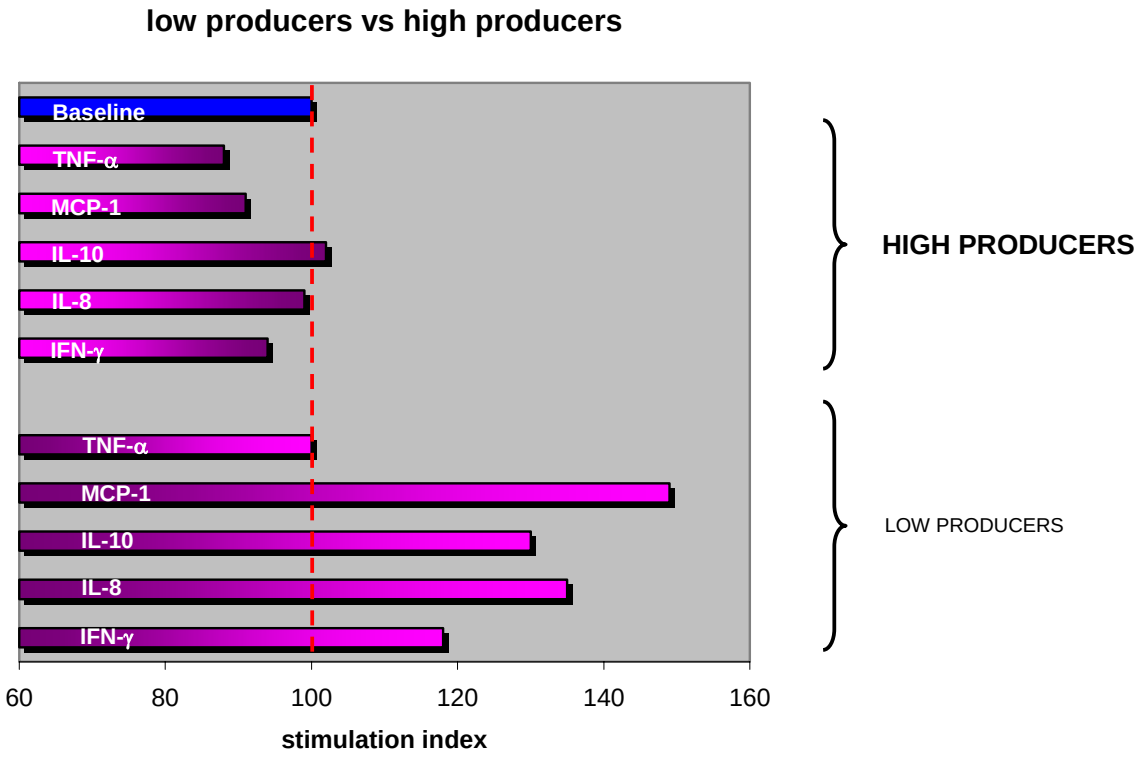

Figure 5 : Echinaforce works as a typical immune-modulator in whereas it induces low responses of mediators which are important in anti-viral defences (IFN-γ), in attracting leukocytes to the site of infection (IL-8 and MCP-1) under concomitant reducing anti-inflammatory processes (IL-10). At the same time TNF-α in high-producers was tendentially reduced.

In subjects with inherent low response of immune mediators Echinaforce® acts supportive whereas in those with already strong response Echinaforce® lowers the production, leading to a more moderate and modulated response.

Summary

First study to show: ECHINAFORCE in vivo works as an IMMUNE MODULATOR

Overall effects

- **Echinaforce has general anti-inflammatory action and induces chemotaxis**
- **It not only has a single target of action but operates in a multiples levels**
- **Immunologically related targets are regulated similarly**

Adaptive effects

- **The actions of Echinaforce develop specifically under particular immunological conditions (adaptive modulation)**
- **In case of susceptibility and stress, when regulatory mechanisms are sparse and when endogenous response is weak, Echinaforce equilibrates and induces mediators.**