Role of ResistAid™ in reducing the occurrence of the common cold

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BACKGROUND

A common cold is a trivial catarrhal infection of the upper respiratory tract (Tyrrell 1996). Acute respiratory diseases are among the most frequent illnesses of all. However, a clinically-relevant, cause-specific (e.g. antiviral) therapy against acute upper respiratory infections is not available at this time. While nutritional and herbal agents have been investigated for their prophylactic effects, and there exists a wide range of cold remedies, treatment of the common cold is still mostly limited to symptom management.
ResistAid™ is a combination of arabinogalactan and natural bioactive polyphenols extracted from larch trees (Fig. 1). Arabinogalactan is a highly branched polysaccharide that is composed of galactose and arabinose units in a 6:1 ratio (Fig. 2).
The immune-enhancing properties of arabinogalactan have been shown in several *in vitro* and *in vivo* studies.
It was found that arabinogalactan enhances natural killer cell cytotoxicity (Hauer & Anderer, 1993). In this study, treatment with arabinogalactan induced an increased release of interferon gamma, tumor necrosis factor α, interleukin 1β, and interleukin 6. Choi *et al.* (2005) investigated the immunomodulating activity of arabinogalactan in mouse spleen lymphocytes and peritoneal macrophages. Incubation with arabinogalactan significantly increased lymphocyte and macrophage cell viability, phagocytosis, lysosomal enzyme activity, and production of nitrite, hydrogen peroxide, tumor necrosis factor alpha and interleukin 6, while having no significant effect on interleukin 1β. A study in dogs demonstrated increases in neutrophils and eosinophils in blood without any effect on serum immunoglobulin G, M or A following oral administration of arabinogalactan (Grieshop *et al.*, 2002).
In a 6-week, double blind, randomized trial (Nantz *et al.*, 2001) evaluating the impact of orange juice fortified with arabinogalactan on the immune system function, a trend towards increased white blood cells and oxidative burst activity was observed. A randomized, double-blind, placebo-controlled study in female subjects (Kim *et al.*, 2002) reported an increase in complement properdin after 4 weeks of treatment with arabinogalactan.
Recently, the immunostimulatory activity of ResistAid™ was evaluated in a randomized, double-blind, placebo-controlled, parallel-group study (Udani *et al.*, 2010). It has been shown that ResistAid™ increased the antibody response of healthy volunteers to the 23-valent pneumococcal vaccine.

Fig. 1: *Larix spp.*

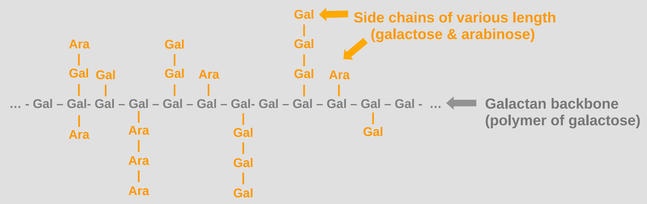

Fig. 2: Chemical Structure of ResistAid™

OBJECTIVE

The aim of this randomized, double-blind, placebo-controlled, parallel-group study was to evaluate the use of ResistAid™ in supporting the body's immune defense against the common cold. The primary objective was to investigate the impact of ResistAid™ supplementation on incidence of cold episodes during a 12 week period as compared with placebo.

Secondary end points included the reduction of episode duration and episode intensity.

Safety and further parameters included the global evaluation of efficacy and tolerability assessed by both the investigators and the subjects and the assessment of adverse events, safety laboratory parameters, additional immunological parameters (leukocyte differentiation) and eating habits.

STUDY DESIGN

During the 12 week study period, 204 subjects who met the inclusion criteria were randomized to the investigational study product (ResistAid™) or placebo. Study supplements were taken once per day at breakfast. The volunteers were instructed to prepare the supplement by dissolving a supplement sachet containing 4.5 grams of ResistAid™ or placebo in approximately 100-150 ml of liquid to drink with their morning meal. All other eating habits were kept unchanged.
A total of 3 basic visits were performed: Visit 1 at study start (= baseline), Control Visit after 6 weeks and Termination Visit after 12 weeks. Additionally, if a cold episode occurred, an Episode Visit was performed at start and on the 5th day of each episode. A cold episode was defined by having (any of) the following symptoms: headache, joint pain, sore throat, difficulty swallowing, hoarseness, coughing, watery nasal discharge, nasal congestion, cold related sleeping difficulties, and body temperature above 38°C.
During an episode, the subjects recorded and assessed their cold symptoms in the subject diary, for a period of 14 days. The diaries were checked by the investigators at the second Episode Visit of each episode.
At study end (Termination Visit), the investigators and the subjects assessed the global efficacy and tolerability of the investigational product.
At the start and end of the study, subjects recorded their eating habits in a diet diary. Further, the safety laboratory parameters as well as additional immunological parameters (leukocyte differentiation) were assessed.

STUDY POPULATION

The inclusion criteria were defined as follows:
- Age 18 – 70 years (child-bearing females had to agree to use appropriate birth control methods)
- Self-reported incidence of at least 3 upper airway infections in a 6 month period
- Written informed consent of the subject

The main exclusion criteria were as follows:
- Acute infection or chronic disease of the upper airways
- Vaccination against influenza or swine flu within 21 days before study start
- Serious organ or systemic diseases
- Clinically significant abnormal laboratory parameters (values outside of reference range)
- Inborn or acquired immune deficiency disease (e.g. HIV infection)
- Pregnancy and nursing
- Use of immunosuppressive or immunostimulating agents as well as antibiotics within 14 days before study start
- Participation in another clinical study at or within 30 days before study start

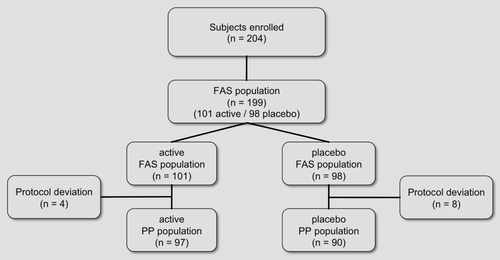

Fig. 3: Flowchart Study Population

In this study, 204 subjects were enrolled at 6 study sites in Germany. 3 subjects terminated the study at screening due to abnormal laboratory values and were excluded from full analysis set (FAS). Another 2 subjects had no data except baseline and were also excluded from FAS. Therefore, the FAS population consisted of 199 subjects.
Due to early study termination and protocol deviations, 12 additional subjects were excluded from the per protocol (PP) set resulting in 187 subjects. The data sets are displayed in Figure 3.

RESULTS

Efficacy endpoints
Intake of ResistAid™ resulted in a reduced mean number of episodes (PP set - verum: 0.85±0.82 vs. placebo: 1.10±0.85; p_U = 0.040; FAS - verum: 0.83±0.82 vs. placebo: 1.06±0.85; p_U = 0.055, Fig. 4a). The total number of episodes was significantly lower in the ResistAid™ group compared to the placebo group (PP set – verum: 82 [n=97] vs. placebo: 99 [n=90]; FAS - verum: 84 [n=101] vs. placebo: 104 [n=98], Fig. 4b).

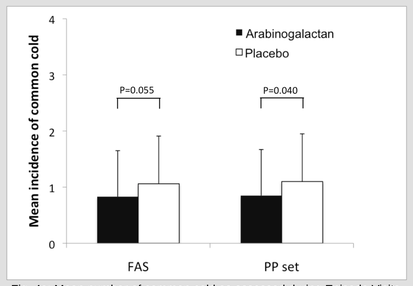

Fig. 4a: Mean number of common cold as assessed during Episode Visits.

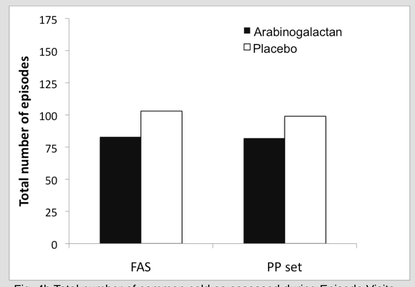

Fig. 4b Total number of common cold as assessed during Episode Visits.

The percentage of subjects who suffered from one or more episodes was significantly higher in the placebo compared to the ResistAid™ group (PP set – verum: 59.8% vs. placebo: 74.4%, p_{Chi} = 0.033; FAS set – verum: 58.4% vs. placebo: 72.4%, p_{Chi} = 0.038; Fig. 5)

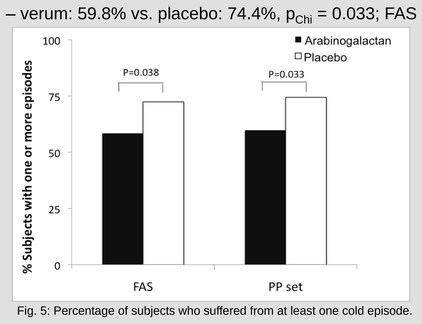

Fig. 5: Percentage of subjects who suffered from at least one cold episode.

There were no differences between the study arms in duration and intensity of cold episodes.
Investigators rated the efficacy of ResistAid™ as "very good" or "good" for 87.8% of the subjects (vs. 75.2% for placebo; p_{Chi} = 0.023; Fig. 6a); 83.7% of the subjects rated accordingly (vs. 73.7% for placebo; p_{Chi} = 0.090; Fig. 6b).

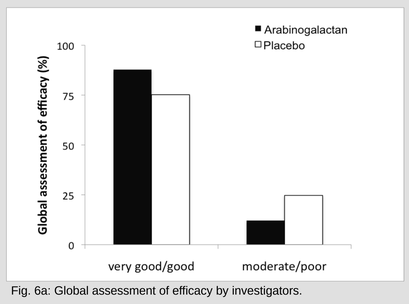

Fig. 6a: Global assessment of efficacy by investigators.

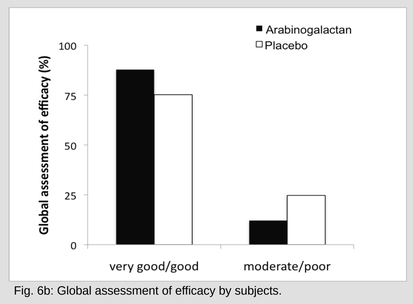

Fig. 6b: Global assessment of efficacy by subjects.

Safety parameters
The global assessment of tolerability both by investigators and subjects was comparable in both study arms. Investigators rated the tolerability of ResistAid™ as "very good" or "good" for 99% of the subjects (vs. 100% for placebo; p_{Chi} = 0.417; Fig. 7a); 98% of the subjects rated accordingly (vs. 99% for placebo; p_{Chi} = 0.487; Fig. 7b). There were no differences between active and placebo group regarding the incidence of adverse events. No changes in the safety laboratory parameters and parameters of leukocyte differentiation were observed.

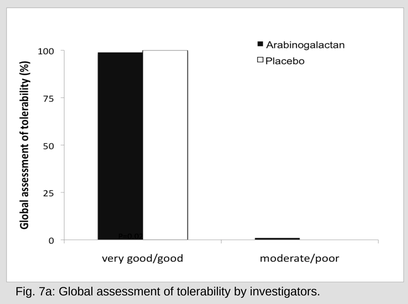

Fig. 7a: Global assessment of tolerability by investigators.

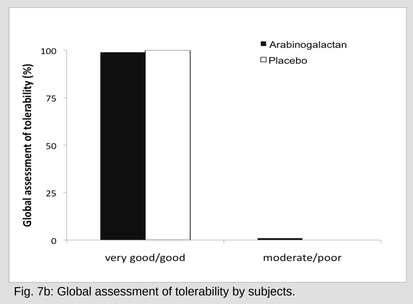

Fig. 7b: Global assessment of tolerability by subjects.

CONCLUSIONS AND DISCUSSION

This randomized, double-blind, placebo-controlled, parallel-group study showed that consumption of ResistAid™ was associated with a significant reduction of the number of cold episodes in comparison with placebo. The supplementation of the arabinogalactan preparation reduced the number of common cold episodes by 23%, which indicates the potential of ResistAid™ to modulate the immune response to invading pathogens.

The present study demonstrated an excellent safety profile of ResistAid™. This is consistent with results of controlled animal studies demonstrating an absence of adverse effects, mortality, and signs of toxicity after oral application of larch arabinogalactan (Groman *et al.*, 1994).
Our study in healthy subjects, representing the general population, confirms the hypothesis of a prophylactic effect of larch arabinogalactan supplementation on the immune system. The data showed, for the first time, the effectiveness of an arabinogalactan preparation to stimulate the human immune system in order to protect against infections caused by pathogens.

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