Andosan™-An Anti-Allergic and Anti-Inflammatory Ingredient Prepared from *Agaricus blazei* Mushroom

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Abstract

Andosan™ is an extract prepared from medicinal *Basidiomycetes* mushrooms, mainly *Agaricus blazei* Murill (AbM) (82%), but it also contains *Hericeum erinaceus* (He) (15%) and *Grifola frondosa* (Gf) (3%), all of which have immunomodulating properties. Whereas He and Gf have been used in traditional Chinese and Japanese medicine against cancer, AbM originates from Brazilian rain forest and was used locally and later abroad as health food for the prevention of a range of diseases, including chronic hepatitis, diabetes and cancer. The mushrooms' health effects are probably due to their content of β-glucans and other smaller immunomodulating polysaccharides and proteoglucans. These effects are mediated through their stimulation of innate immune cells, such as monocytes, NK cells and dendritic cells, and the amelioration of a skewded Th1/Th2 balance and of inflammation. Here, we give an overview of the anti-allergic effects of Andosan™ in a mouse model for allergy and anti-inflammatory effects both in vitro, in healthy individuals and in patients with inflammatory bowel diseases.

Keywords: Andosan™; *Agaricus blazei*; Allergy; Inflammation; IBD

Introduction

Atopy is a condition where the immune system reacts to common substances in the environment (allergens) with a genetically determined overproduction of allergen specific antibodies of IgE isotype. This reaction is known as the type-I hypersensitivity reaction according to Coombs and Gell. The atopic phenotype can simply be characterized as the dominance of the Th-2 type over the Th 1 type immune response. Allergic inflammation is the important part of the type-I allergic reaction. Why atopic individuals react to common allergens with the Th-2 mediated mechanism is not entirely known. Influence of colonisation with different intestinal microbiota during early infancy, impact of early infant nutrition, exposure to allergens and other little-known factors of prenatal and postnatal period are hypothesized.

The clinical units of so called atopic disease are allergic rhinitis (rhinoconjunctivitis), allergic bronchial asthma and atopic eczema. Allergies to insect venoms and drugs are not considered to be due to the atopic phenotype and heredity does not seem to play an important role in the disease manifestation.

Atopic diseases affect approximately 20-25% of the population in the developed countries resulting in diagnosis and treatment of atopy being a major health political problem. For these reasons, scientists are looking for methods of early diagnosis and effective prevention of atopic disease. Although some prophylactic measures have been documented to have some limited effects (e.g. restriction of passive smoking, prolonged breastfeeding) on the development of atopic disease, until now, there are no measures known that provide a cheap, efficient, simply accessible and long lasting protection against development of atopy.

Immunomodulation in atopic disease

The aim in the prophylaxis and treatment of atopy is to reverse the Th-2 dominated atopic phenotype back to the non-atopic Th-1 phenotype and thus to eliminate or alleviate clinical symptoms of the underlying atopic disease. Immunomodulation may be largely specific, where known allergens are administred to patients in order to achieve specific tolerance. This is the case in the allergen-specific immunotherapy (ASIT). Because during the allergen-specific immunotherapy allergen extracts from natural sources (e.g. pollen extracts) are used, it can be speculated that the overall effect of ASIT can be attributed to a combination of allergen-specific tolerance induction and a nonspecific immunomodulation by not exactly characterized additional carbohydrate substances. Another form of immunomodulation used in the treatment of atopic disease is the biological therapy, where monoclonal antibodies directed against IgE molecules are used, the so called anti-IgE therapy. This treatment is currently the only approved and used non-allergen-specific immunomodulatory treatment of atopy.

Other ways of non-specific immunomodulation of atopic disease are so far experimental. These include downregulation of the whole immune system targeting the adhesion molecules, therapies targeted towards Th-2 specific cytokines, cytokine receptors or chemokine receptors, and interfering with signaling pathway molecules [1]. These treatments show promising results but they are certainly expensive and possibly limited to a small group of patients. Thus, immunomodulation by food or food supplements still remains a very exciting form of possible atopy treatment. Immunomodulation by food has the advantages of simplicity, low side effects and greater

accessibility for low-income population groups. Results of in vitro experiments have demonstrated immunomodulatory effects of fungal β-glucans [2,3] and are described in details below. Moreover, positive effects of immunomodulation by food have already been described in humans [4]. Specifically, Talbott [5] and Yamada [6] documented positive effects of supplementation of β-glucans on symptoms of pollen allergy. Results of the above studies demonstrate the anti-allergic and anti-inflammatory properties of fungal immunomodulators and give hope for the future that they could be increasingly used in the treatment and prevention of atopy in larger populations.

Inflammation

Inflammation is a physiological state related to antimicrobial defence and tissue repair. However, inflammation becomes a disease when it is chronic and unrelated to the above, as it is in immune-related diseases such as inflammatory bowel disease (IBD) and rheumatoid arthritis. IBD, ulcerative colitis (UC) and Crohn's disease (CD) is evenly distributed between the sexes and mostly affect age groups 15-35 years. UC is an inflammation solely of the colonic mucosa whilst CD may be transmural involving all layers of the intestinal wall of the large and small bowel, but, more seldomly, the gastrointestinal tract from duodenum to the oral cavity. In UC there may be a continuous inflammation and microscopically the entire colon is often affected, whilst in CD healthy and diseased patches of bowel are often interspersed. The diseases are characterised by chronic and relapsing inflammation that may cause anorexia, weight loss, diarrhea, pain and fever. Moreover, in CD malabsorption and subileus occur from small bowel stenosis and the transmural inflammation can cause fistulisation to other epithelial lined organs. Common to both diseases are extraintestinal manifestations; iridocyclitis, spondylitis and inflamed joints with a preponderance in CD. The development of IBD is though to originate from a combination of genetic and environmental factors. Thanks to genetic studies, IBD is now perceived as diseases with immune reactions against bowel bacteria in genetically predisposed individuals [7]. Key insights from gene discovery include the role of IL-23/Th-17 signalling in IBD and defective processing of intracellular bacteria in CD, resulting in compensatory increased Th1 cell activity [8], and defective barrier function in UC [9], which has been associated with increased Th2 responses in that disease. For both diseases an unselective increase in the colonic mucosa of chemokines (MIP-1ß, MCP-1, IL-8) [10] and cytokines IL-1ß [11], IL-6 and TNFα [12] have been demonstrated. In serum, however, fewer cytokines are studied, but increased levels of IL-6 and TNFα were detected in both diseases, whilst increased MIP-1ß was found in UC [13]. Gastroenterologists have been searching for improved treatment opportunities for IBD patients who in severe cases end up with colectomy (UC patients) or very costly anti-TNF (Remicade or Humira) treatment (mostly CD patients), which often must be discontinued due to serious side effects mainly from opportunistic infections (e.g. *Pneumocystis carinii* pnemonia, tuberculosis) in 29-38 % but also from congestive heart failure in 0.4-0.8 % of the patients, respectively [14,15] as well as resistance to treatment. Other side effects are increased risk for melanoma (OR 1.8) [15] like demyelination, aplastic anemia, intestinal perforation, systemic lupus and lymphoma affected the patients in the range of 0.02–0.8 % [14].

Photo: NutriCon ©

Agaricus blazei cultivated in Piedade, Brazil. photo G Hetland 2012

Figure 1: *Agaricus blazei* Murill cultivated commercially for the health food market in Japan (A) and in a nursery in Brazil (B).

Edible mushrooms, foremost of the *Basidomycetes* family have had a long and successful medicinal use especially in traditional Chinese and Japanese medicin. Today, approximately two million people in Japan consume *Basidiomycetes* mushrooms such as *Agaricus blazei* and *Ganoderma lucidum* as an immune response modifier for prevention of cancer or as nutritional support during chemotherapy and for chronic inflammatory conditions such as hepatitis (commun. Dr. V Badmaev, Badmaev Natural Drug Foundation, NY). Medicinal herbs have been used in traditional medicine based on empiric observations and their use has scientific merit because many active substances with specific medical applications have been identified in such herbs, e.g. acetyl salicylic acid, atropin, digitoxin and morphine.

Examples of substances derived from fungi are the antibiotics, penicillin and griseofulvin, and the immunosuppressant, cyclosporine A, that has enabled organ transplantation. In mushrooms the macrofungi substances with a range of therapeutic effects have been detected [16], including chemically highly diversified anti-inflammatory compounds, which include polysaccharides, terpenoids, phenolic compounds, and other lowmolecularweight molecules [17].

Agaricus blazei Murill (AbM), first described in 1893 as *Agaricus subrufescens* and also known as *Agaricus rufotegulis* [18] is related to the champignon (*Agaricus bisporus*). It was rediscovered in 1970 growing naturally in a coastal rain forest area near Piedade in Southern Brazil where it was used as food and also against cancer and various diseases [16]-hence it became also known as *Agaricus brasiliensis* [19]. Later, this mushroom was taken to Japan for cultivation as health food (Figure 1A) [18], but it is now also cultivated locally in Brazil for commercial purposes (Figure 1B). The particular mushroom extract brand Andosan™ discussed here, is a well-defined mixture of extracts from the *Basidiomycetes* mushrooms AbM (sub-species Heineman) (82.4%), *Hericium erinaceus* (synonym: *Hericium erinaceum*) (He) (14.7%), and *Grifola frondosa* (Gf) (2.9%), grown in Gifu-ken, Japan, and developed by ACE Co. Ltd., Japan, in collaboration with researchers at the nearby Shinshu University, Faculty of Agriculture, in Nagano-ken, Japan.

There are many studies on the immuno-modulating properties of *Agaricus blazei* Murill (AbM) and also pre-clinical and a few clinical reports on effects of AbM against cancer, chronic hepatitis and diabetes [20,21]. Both He and Gf have been used in Chinese medicine against cancer, which is also found in mouse models [22,23] in addition to immunomodulatory properties [24,25]. Thus, some of the traditional medicinal uses of these mushrooms have been documented. The anti-allergic and anti-inflammatory research with *Basidiomycetes* and Andosan™ are discussed in this review, which is based on 1st authors presentation at the Immuno Summit 2014 meeting in Baltimore.

Mechanism of Action-Immunomodulation

The fruiting body of AbM is rich in immunomodulating β-glucans [26], which is main part of the cell wall cytoskeleton in yeast, fungi and mushrooms. Such β-glucans have been found to have anti-cancer and anti-infection effects when given i.p. in mouse models [26-29]. AbM has adjuvant effects in hepatitis B virus and foot-and-mouth disease DNA vaccines in mice owing to humoral and cellular responses [30,31].

AbM is shown to have antitumor effects against fibrosarcoma, myeloma, and ovarian-, lung-, colon- and prostate cancer in mouse models [32-36]. In patients with gynecological cancer, placebo-controlled AbM add-on treatment to chemotherapy was reported to increase NK cell activity in blood and improve the patients quality of life [37]. At Oslo University Hospital (OUH) Dr. Tangen and colleges have studied patients with multiple myeloma undergoing high-dose chemotherapy, given add-on placebo-controlled treatment with the AbM-based Andosan and found immunomodulatory effects: There was reduced IL-1β receptor antagonist levels in plasma indicating anti-inflammatory effect, and increased T regulatory cells and plasmacytoid dendritic cells (DC) in blood as well as increased expression of genes for killer immunoglobulin receptor and MHC antigens, which are important for antigen presentation [38]. Although such a trend was

noted, too few patients were included in that study to show significantly improved survival or increased time to new treatment.

The effects above are brought about by AbM stimulation of monocytes, granulocytes and NK cells via TLR2 [39], and probably dectin-1 and CD11b/18 [40-42], giving increased cytokine production [43,44], upregulation of adhesion molecules on leukocytes [45], and dendritic cell activation [46,47]. In vitro stimulation of monocytic cells by Andosan AbM extract has shown increased expression of genes related to immune function [48]. Of special interest for our study of inflammatory bowel inflammation is upregulation of the gene for IL-23. In vivo, oral intake of Andosan for 7 days by a few patients with chronic HCV infection gave an insignificant reduction of HCV load in blood but increased the expression in peripheral mononuclear leukocytes of genes related to G-protein-R-signalling, cell cycling and transcriptional regulation [49]. While G protein–coupled-receptors are for chemotaxins such as IL-8 chemokine, leukotriene 4B, the complement activation product C5a and bacteria-derived formyl peptides and are associated with inflammation and microbial defence, the regulation of cell cycling and transcription is rather linked to tumor defence.

The reason for the observed forceful and swift engagement of innate immunity and subsequently scewing of adaptive immunity away from Th2 and towards Th1 responses when encountering contact with an edible and harmless mushroom such as AbM, is its shearing of pathogen-associated molecular patterns (PAMP) with other highly poisonous and health-threatening fungi and the bigger fungi; mushrooms. Such fungi and mushrooms are usually a health threat because of the action of their toxins; e.g. muscimol from *Amanita muscaria* and the vasoconstrictor ergotamine from *Calviceps purpurea*, or invasion in immune-deficient patients (e.g. *Aspergillus fumigatus*) or normal individuals (e.g. *Stachybotrys chartarum*). PAMP, such as β-glucans form the main cell wall skeleton in mushrooms and fungi are recognized immediately by so-called pattern-recognition receptors (PRR), such as TLR2, dectin-1 and CR3 [41,42,50]. However, the anti-allergic effects of Andosan, descibed below, are most probably not due to β-glucans because we have previously found that β-glucans from yeast rather increased the allergic response to ovalbumin in mice [51]. As suggested below, smaller molecules may be responsible for these effects. The anti-allergic effect of AbM confirmed by others in OVA-sensitized mice, was concluded as being due to activation of macrophages by epithelial cells and a subsequent differentiation of naïve T cells into Th1 cells [52]. The proposed anti-inflammatory effect of Andosan agrees with the antitumor properties of AbM because inflammation is a driving force in cancer, which has a tendency to develop following local chronic inflammation, e.g. colon cancer after ulcerous colitis, hepatocellular carcinoma after chronic hepatitis, pancreas cancer after chronic pancreatitis etc.

Pharmacokinetics and Potential Drug-Herb Interactions

There is a general problem regarding up-concentration in mushrooms of heavy metals, which becomes evident if they are cultivated on poluted soil, and also of radioactivity, which became well-known after the Tchernobyl catastroph when there was restriction on consumption of meat from reindeer and sheep grazing in areas with radioactive fall-out. There are conflicting opinions concerning the safety of agaritine, a hydralazine-containing compound, that is found in AbM. Whereas one report says it may be

toxic and cancerogenetic in animals [53], another documents agaritine as an anti-tumor substance against leukemic cells [54]. Moreover, a toxicity study over two years in rats rather found that animals ingesting the highest AbM concentration lived the longest, presumably due to reduced cancer development [55].

Herb-drug interactions are associated with cytochrome P-450 metabolism and the trans-membrane efflux pump P-glycoprotein (P-gp) that is present in normal intestinal lumen where it may limit drug absorption, as well as in the liver, where it may increase excretion of the drug [56]. Among other herbal remedies, a fermented extract of the *Agaricus blazei* Murill (Gold Label) from Japan that was later trade marked as Andosan™, was investigated at the Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway, for in vitro inhibitory potential on P-gp-mediated transport of digoxin in the Caco-2 intestinal cell line. It was found that AbM (3.8 mg/ml) inhibited P-gp (i.e., net digoxin flux (IC_{50})) in vitro in a similar concentration as did green tea, without affecting viability of the cells [56]. Hence, AbM may interact with P-gp substrates such as: vinblastine and vincristine anticancer agent, digoxin cardiac agent, cyclosporine immunosuppressive agent [57] and loperamide anti-diarrhea agent-hence, it should not be given to individuals using such drugs. AbM should also not be given together with other P-gp inhibitors such as verapamil and quinidine.

When the same researchers tested this particular AbM extract for in vitro inhibition potential on cytochrome P-450 (CYP3A4 isoform) metabolism, it was found to inhibit it (IC_{50}: 1.3 mg/ml) but 20 times less than did green tea [58]. The P-450 enzyme is involved in the metabolism of 50% of drugs [59] and is therefore also of interest for drug-herb interactions, especially with regard to cytotoxic chemotherapeutics that have narrow therapeutic windows [60]. Researchers Engdal and Nilsen [58] concluded that, "although *Agaricus* (read: Andosan™-then known as Agaricus Gold Label from ACE Co, Japan) inhibited CYP3A4 (read: cytochrome P-450 metabolism) in vitro, clinical relevant systemic or intestinal interactions with CYP3A4 were considered unlikely. Moreover, Andosan has also been tested at an Olympic committee-approved anti-doping facility in Oxford (HLF Sport Science), and found by liquid chromatography to be free of any of the 130 illegal substances on the international anti-doping drug list, and further by gas chromatography to be free of steroids and thus cleared for use against injury- and exercise-related inflammation by competing athletes. Hence, Andosan does not contain any of the above substances on the anti-doping list, some of which may interfere with other drugs.

Allergy

Mould and fungi are risk factors for allergy and asthma in damp indoor environments or when used as insecticid [61,62] and have been shown to adjuvate allergy development in a mouse model [51]. When working at The Norwegian Institute of Public Health, Oslo, and searching for new principles for combating allergy/asthma and multi-resistant infections, G Hetland set out to examine possible anti-allergic properties of immunomodulating substances used for chronic infections in traditional medicine and health food. The approach was based upon the Th1/Th2 dichotomy hypothesis [63], saying that a putative immunomodulating substance with anti-microbial effect would do so by inducing or enhancing a Th1 response that would result in a reciprocal reduced Th2 response in the individual. Since there has been much focus in Japan on medicinal benefits of AbM, it was of interest to examine this mushroom in the allergy model.

However, since the mouse allergy model is more cumbersome then the rapid and robust pneumococcal sepsis model in mice [29], the latter was employed to screen for biological activity of new substances. Hence, we compared in a blinded fashion the efficacy of 5 different AbM extracts from main Japanese producers of health food in the bacterial sepsis model in mice, using S. *pneumoniae* 6B i.p. for challenge. In this comparison, only extract A gave a significant reduction in bacteremia and increase in survival vs saline (PBS) control (p<0.05) [40] (Figure 2), so this extract was chosen for further work in the allergy model and then for human studies later on after it had been labeled Andosan™.
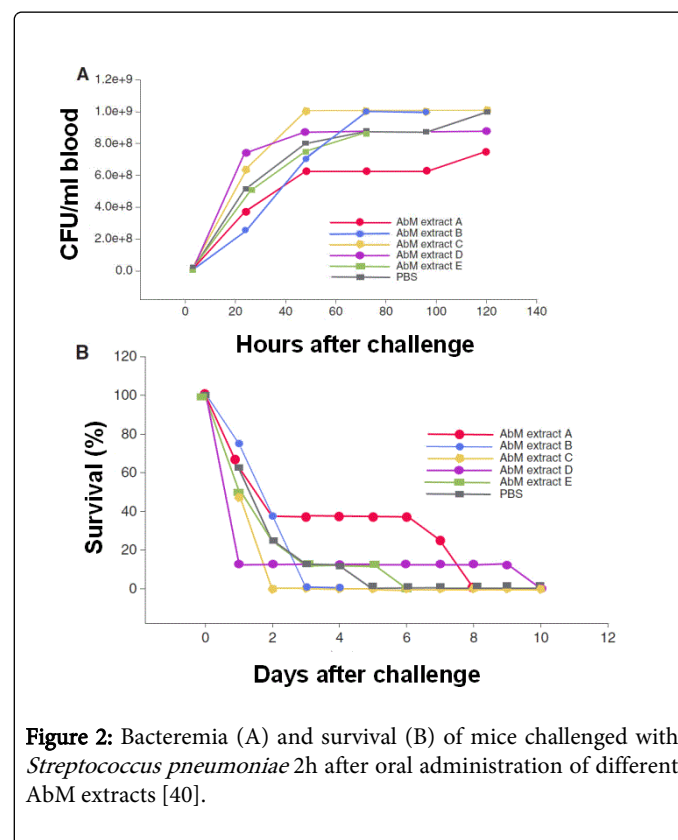

Figure 2: Bacteremia (A) and survival (B) of mice challenged with *Streptococcus pneumoniae* 2h after oral administration of different AbM extracts [40].

As described by the scheme for the experiments in the murine allergy model, Andosan™ or PBS was given p.o. 1 day before or 3 weeks after immunization s.c. with the model allergen, ovalbumin. After 26 days the mice were sacrificed, bled for serum, their spleens removed, and the spleen cells cultivated 1 day further with Andosan or phosphate-buffered saline (PBS) (Table 1) [64]. ELISA analyses were used for specific anti-ovalbumin IgE (Th2 response) or control IgG2a (Th1 response) antibodies in serum, and IL-4 and IL-5 Th2 type cytokines, and IL-2 and IFNγ Th1 type cytokines in spleen cell culture supernatants.

We found that Andosan™ AbM-based extract protected against allergy in mice because there was less IgE antibodies (Th2 response) against the ovalbumin allergen in mice given Andosan™ before ovalbumin immunization (Figure 3) [64]. There was also a tendency to more control IgG2a antibodies (Th1 response in the mouse) against ovalbumin in mice given Andosan™ before the ovalbumin immunization. Moreover, since there were significantly less IgE antibodies against ovalbumin in mice given Andosan™ after ovalbumin immunization, the mushroom extract also had a therapeutic effect on

OVA allergy. The effect of Andosan in cultures of spleen cells from the animals above was the following: We observed significantly less Th2 cytokines (IL-4 and IL-5) relative to Th1 cytokines (IL-2 and IFNγ) in spleen cell cultures from ovalbumin-sensitized mice that were given Andosan™ AbM-based extract either before or after the ovalbumin immunization [64].

Exp#	#Mice per group, strain	Treatment D-1 (pre-OVA) (200 µl gavage)	Immunization D 0 OVA (10 µg)+ Al(OH)3 s.c.	Treatment D 19 (post-OVA) (200 µl gavage)	Boosting D 20 OVA (10 µg) s.c.	Sacrifice D 26 Harvest
1	16 NIH/OlaHsd	AndoSan/PBS p.o.	Taibase	-	Taibase	Serum, spleen
2	16 NIH/OlaHsd	-	Taibase	AndoSan/PBS p.o.	Taibase	Serum, spleen
3	08 NIH/OlaHsd	AndoSan/PBS/dialysed Andosan p.o.	Taibase	AndoSan/PBS p.o.	Taibase	Serum

**Table 1:** Experimental design for murine allergy model
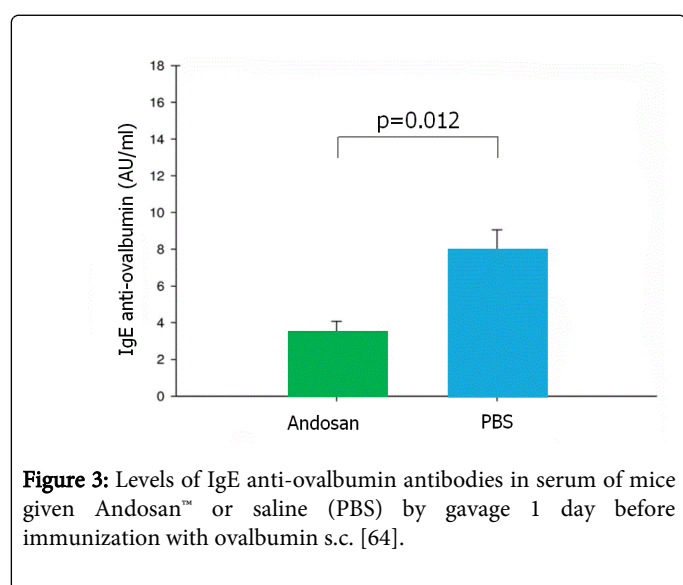
Figure 3: Levels of IgE anti-ovalbumin antibodies in serum of mice given Andosan™ or saline (PBS) by gavage 1 day before immunization with ovalbumin s.c. [64].

When prior to OVA sensitization the mice were given Andosan™ that had been dialysed against a membrane with cut-off 12.5 kD, the observed reduction in specific IgE anti-OVA antibodies in serum was rendered not statistically significant (Figure 4). Hence, small molecular substance(s) in Andosan contribute(s) to its anti-allergy effect. Such substances are not β-glucans, both because they are usually bigger molecules and because we have previously shown that a β-glucan from yeast rather had a positive adjuvant effect on OVA sensitization in the very same allergy model in mice [51]. Moreover, Andosan has been shown to contain far less β-glucans than anticipated [65], which probably is due to the fact that it is an extract of the mycelium of the three *Basidiomycetes* mushrooms and not of their fruiting bodies, which for AbM is reported to be rich in β-glucans [26]. Therefore, most probably also the anti-inflammatory effect of Andosan must be caused by other immunomodulatory substances than β-glucans. Together with researchers at Norwegian University for Life Sciences at Aas, we are currently characterizing protein fractions in the Andosan extract and examining their biological properties.

Our findings agree with the AbM-mediated amelioration of skewed Th1/Th2 balance also observed in asthma-induced and fibrosarcoma-bearing mice by oral administration of *Agaricus blazei* extracts [66]. There has been no clinical trial so far using Andosan as a supplement

in the treatment of atopic disease, but the outcome of such an investigation would have been very interesting.
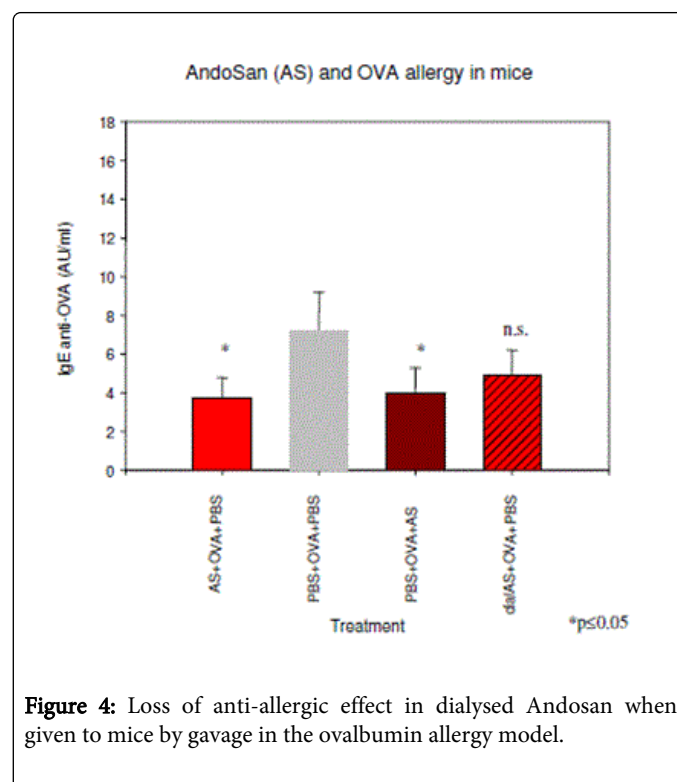
Figure 4: Loss of anti-allergic effect in dialysed Andosan when given to mice by gavage in the ovalbumin allergy model.

Inflammation

When examining the safety of Andosan intake in healthy volunteers, E Johnson and colleges detected that in contrast with the pro-inflammatory findings in vitro [67], this mixed mushroom extract did in fact have anti-inflammatory properties in vivo. After 12 days oral treatment with Andosan there was a significant decrease in serum levels of the pro-inflammatory cytokines IL-1β, TNFα and IL-6, in addition to IL-2 and IL-17 (Figure 5). Also, there were no pathological findings in blood tests for liver-, pancreas- or kidney function and no detectable clinical side effects.
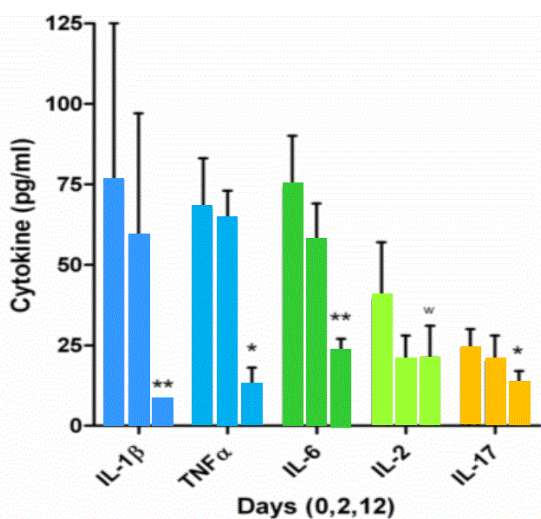
Figure 5: Phase I study in healthy individuals given 60 ml/day of Andosan™ orally for 12 days and cytokines measured in blood samples [67].

Based on the anti-inflammatory findings in healthy volunteers, patients with IBD; Ulcerous colitis and Crohn's disease, were then treated with Andosan in a pilot study at Oslo University Hospital, Departments of Gastroenterologial Surgery and Medicine [68]. After 12 days of Andosan ingestion there was a significant decline in LPS-stimulated blood samples ex vivo of pro-inflammatory cytokines MIP-1β, MCP-1, IL-8, IL-6 and IL-1β and growth factors (Figure 6 and 7). Interestingly, in CD also IL-17, which part-takes in the pathogenesis of the disease, and the Th-1 cytokine, IL-2, were reduced (Figure 7). The decreased level of IL-17 disagrees with our finding of increased expression of the IL-23 gene in Andosan stimulated monocytic cells [48]. However, that was in vitro experiments which cannot be readily used for in vivo application. Moreover for UC we found less fecal calprotectin after consumption of the mushroom extract. Some patients, although not systematically studied, even noted reduction of symptoms including less diarrea and joint pain. Altogether, these results pointed towards an anti-inflammatory effect of Andosan in the IBD patients, without detection of any potential side effects.

In a placebo-controlled, single blinded trial in 100 IBD patients (50 UC and 50 CD), at OUH, Ulleval 2014 (Therkelsen et al., manuscript in preparation) 25 patients in each group used Andosan or placebo for 3 weeks. The patients were examined prior to, during and after intake of Andosan or placebo with regard to disease symptom score and quality of life as well as with blood samples for cytokines (not analysed yet) and more. Preliminary analysis of the results indicate improvements of clinical symptoms and fatigue after Andosan™ consumption.
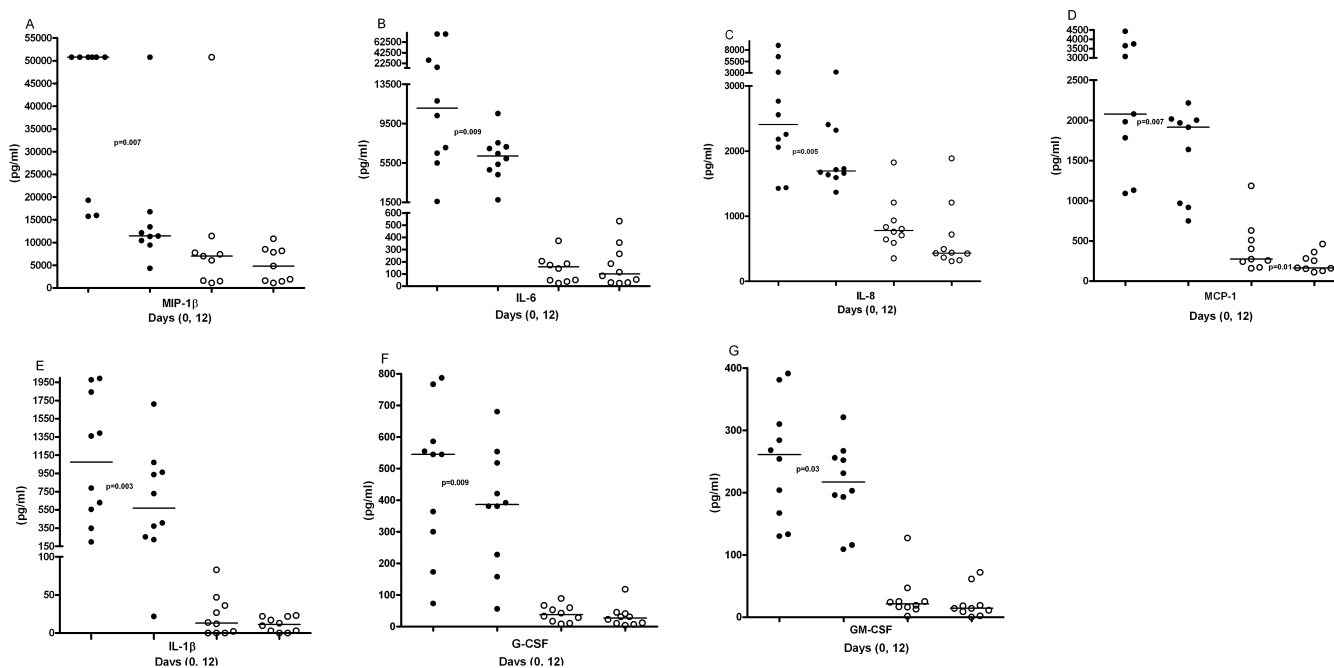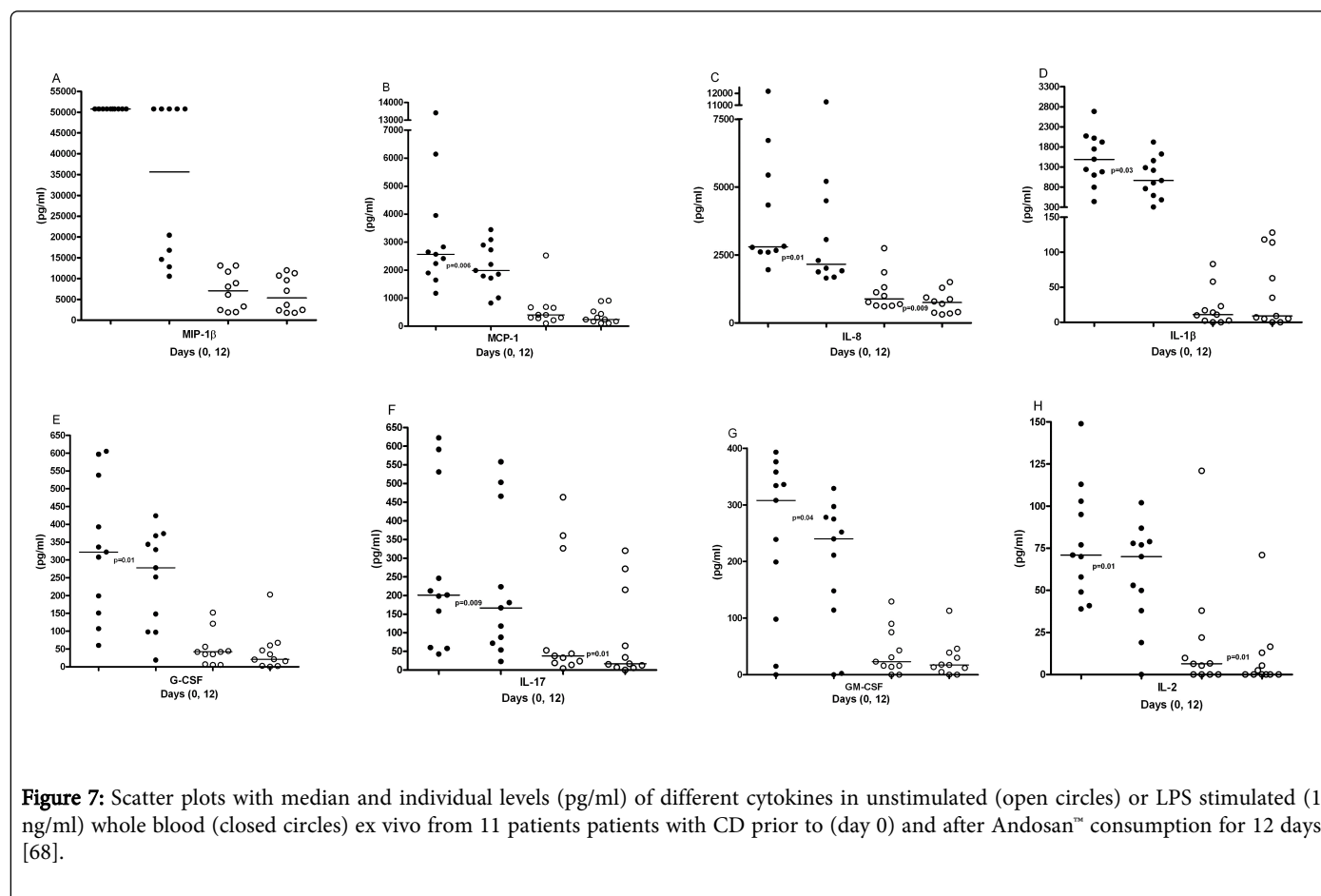

Figure 6: Scatter plots with median and individual levels (pg/ml) of different cytokines in unstimulated (open circles) or LPS stimulated (1 ng/ml) whole blood ex vivo from 10 patients patients with UC prior to (day 0) and after Andosan™ consumption for 12 days [68].

Legumain (asparaginyl endopeptidase) is a proteolytic enzyme that is prominently expressed in mammalian tissues and solid tumors [69]. We have recently found that Andosan and isolated carbohydrate fractions thereof inhibit the activity of the tumor-associated and proinflammatory protease, legumain in macrophages [65].

Another indication of the anti-inflammatory effect of Andosan, is its effect in top athletes who experience inflammation after hard training and injuries. Swimmers and Nordic skiers also tend to develop exercise-related asthma. Moreover, since AbM extract improved quality-of-life in a clinical study with cancer patients on chemotherapy [37] and chemotherapy similar to strenuous exercise

breaks down tissues before regeneration, elite swimmer Alex Hetland suggested that an AbM extract such as Andosan may also help improve restitution during tough training periods. He tested this out in a survey with his team of professional swimmers at Club Wolverine, Ann Arbor, MI, USA in the 2011/2012 winter training before London Olympics and the World Swim Championship in Istanbul, Turkey, the same year. The results after 3 months' intake of Andosan™, which had been cleared by an approved UK anti-doping laboratorium, was improved recovery after training, less illness and improved performance [70].

Figure 7: Scatter plots with median and individual levels (pg/ml) of different cytokines in unstimulated (open circles) or LPS stimulated (1 ng/ml) whole blood (closed circles) ex vivo from 11 patients patients with CD prior to (day 0) and after Andosan™ consumption for 12 days [68].

Conclusions

Our report agrees with AbM-induced anti-inflammatory and anti-allergic effects found in mouse bone marrow-derived mast cells [71], the inhibitory effect on mast cell-mediated anaphylaxis-like reactions in mice [72], and the amelioration of skewed Th1/Th2 balance in asthmatic [66] and allergic mice [52]. On the other hand, it disagrees with reports on proatherogenic and proinflammatory effects of AbM in a mouse model for atherosclerosis [73] and a clinical randomized trial that found no immunomodulatory effect in elderly women who received dried AbM extract [74]. However, most of the literature supports the anti-inflammatory and anti-allergic findings done with the AbM-based Andosan ingredient. In line with this and the autoimmune aspect of diabetes [75] is also the observations that AbM ameliorates diabetic disorders in murine models [76,77], as well as in a clinical study on insulin resistance type 2 diabetes [21].

The overall role of Andosan in immuno-modulation and disease control seems to be the stimulation via specific receptors of antigen-presenting cells such as monocytes and dendritic cells, giving an increased Th1 and reciprocal decreased Th2 response resulting in enhanced attack on microbes and tumor cells and lower allergic and asthmatic reactions. The tumor attack is enhanced by the activation of NK cells and the antigen-presentation by the upregulation of MHC antigens on leukocytes. The anti-inflammatory effect of Andosan is evidenced by the anti-allergic effect in a mouse model, the reduction in proinflammatory cytokines in serum of both healthy individuals and IBD patients. In addition, the mushroom extract reduced activity of the tumor-associated and proinflammatory protease legumain, in vitro, and seemed to improve restitution in athletes and be beneficial for exercise-related asthma. In the IBD patients, the decline in pro-inflammatory cytokines detected in plasma must be partly responsible for the improvements observed in their clinical symptoms. How

Andosan actually influences Th1/Th2 responses and IL-23/Th17 signalling in IBD patients, will be revealed in the newly finished placebo-controlled clinical study in 100 UC and CD patients by Therkelsen and collaborators.

Disclosure

G Hetland is co-founder of Immunopharma AS, Norway, which aims at developing Andosan into adjuvant hospital treatment for patients with severe and non-curable diseases. The other authors have no interest to declare.

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