
G. Hetland¹, E. Johnson²,³, D.M. Eide⁴, B. Grinde⁵, A.B.C. Samuelsen⁶ and H. G. Wiker⁷,⁸

¹Depts of Immunology and Transfusion Medicine, ²Gastroenterological and Pediatric Surgery, Oslo University Hospital, ³Inst of Clinical Medicine, Medical Faculty, and ⁴School of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Oslo, ⁵Dept of Environmental Medicine and ⁶Mental Health, Norwegian Inst of Public Health, Oslo, and ⁷Dept of Microbiology, Haukeland University Hospital, Bergen and ⁸The Gade Research Group for Infection and Immunity, Dept of Clinical Science, Faculty of Medicine and Dentistry, University of Bergen, Norway.

The increasing occurrence of multi drug-resistant (MDR) pathogenic microbes is a threat to the public health and prompts a call for novel antimicrobial strategies. In Eastern traditional medicine edible mushrooms have been used for over 3000 years against a range of diseases including infections. β-glucans from yeast and mushrooms and pectin from Plantago major L. have anti-infectious properties in rodent models against different microbes, including mycobacteria. The medicinal mushroom Agaricus blazei Murill, used traditionally against cancer and hepatitis, has been found to have antitumor effects in mouse models. An Agaricus extract, Andosan™, also containing two related mushrooms has been shown to protect against both Gram-positive and -negative sepsis in mice and has been tested against viral infections, as reviewed here. Thus, in the future, biologically active substances isolated from medicinal mushrooms and plants, may prove useful alternatives in the fight against serious infections by MDR pathogens.

Keywords MDR microbes, pneumococci, fecal bacteria, mycobacteria, β-glucan; Plantago major L., Agaricus blazei Murill, Andosan™

1. Introduction

Besides the well-known hospital tormentor, methicillin-resistant Staphylococcus aureus (MRSA), life-threatening bacteria such as Mycobacterium tuberculosis, Streptococcus pneumoniae and others are becoming MDR, suggesting that the microbes may win the battle over antibiotics. That would not be surprising because microbes have been on this planet far longer than humans and have survived huge climate changes and are today adopted to life in quite different habitats, e.g. thermic bacteria in Yellowstone geysers and in volcanoes that live on sulphur, pressure (>1000x atmospheric pressure)-resistant bacteria in the sub-sea Mariana depression in the Pacific ocean near Guam [1], anaerobic bacteria in the gut etc. The mechanisms for development of MDR in microbes under repression of bacteriostatical or bactericide drugs, include lateral transfection of other strains and species of bacteria by plasmids containing genes for drug resistance. One reason is unwise over-use of antibiotics for infections, also most probably viral ones such as those causing otitis media in small children, or under-use - too low doses or shortened antibiotics administration. The MDR infection epidemic is of great concern to the public health and new strategies are called for to regain the upper hand in this battle.

In Eastern and African traditional medicine edible mushrooms and medicinal herbs have been used for thousands of years against a range of diseases including infections, which is still the major health threat in Africa. This empiric knowledge is very little tapped into by Western medicine and it is therefore pertinent to exploit this field in search of drugs novel to Western societies that may supplement or adjuvate our current hospital therapies for infectious diseases and also in other disciplines. Especially, it is of interest to activate the innate arm of the immune system because it is evolutionary old and shared with sea urchin, sebra fish and banana fly, and thus has been successfully exploited in other and more ancient species than ours. Many fungi and mushrooms are lethal to insects, animals and humans and we have therefore developed specific receptors, e.g. toll-like receptor 2 (TLR2), on immune cells for the common fungal signature molecule, β-1,3-D-glucan, that is the main structural ingredient of the cell wall of fungi and mushrooms. β-glucan are also found in some bacteria and plants [2]. We share TLR with the banana fly, Drosophila melanogaster, in which these receptors were detected in 1985 [3] and with rodents and other mammals. Other non-TLR receptors that may be involved are dectin-1 and the lectin-binding site in CD11b/18 (complement receptor 3). Most probably fungi and mushrooms also contain other such so-called pathogen-associated molecular pattern substances that may similarly activate a native immune response in the host against potential danger. Therefore, β-glucans and other immunomodulating molecules in fungi and mushrooms represent danger signals that trigger cells of the innate immune system against potentially lethal attack from the outer world. β-glucans are D-glucose polymers linked by β-glycosidic bonds. The structures of two different types of β-glucans are shown in Fig. 1. SSG (scleroglucan) is a soluble, although viscous, gel-forming and highly branched β-glucan with high molecular weight (>5x10⁶ kD) from the culture broth of the fungus Sclerotinia sclerotiorum [4]. In Japan similar β-1,3-glucans from mushrooms such as lentinan, have been
used in combination with chemotherapy to treat cancer patients for more than 30 years [5]. MacroGard® is a β-1,3-glucan extracted from baker’s yeast with less frequent side-chains but that contain more than two glucose molecules. It is a potent immuno-stimulant produced in both a soluble and particulate form [6]. Others and we have found that harmless substances such as β-glucans and the edible Basidiomycetes mushroom, Agaricus bM, can be exploited to enhance the immune response against invading and dangerous microbes both of extracellular, e.g. E.coli [7] and pneumococci [8,9], and obligate intracellular nature, e.g. mycobacteria. The anti-mycobacterial properties of β-glucans have been proven both for M. tuberculosis-infected macrophages in vitro [10] and in a M. bovis, BCG model in mice [11]. Similar to β-glucans, Agaricus bM is also found to stimulate TLR2 [12].

Actions of innate immunity are swift, powerful and general and may thus be effective against different infections - MDR ones or not. β-glucan is a structural polyglucose in the cell wall of yeast and mushrooms with known immunomodulatory, antitumor and anti-infection effects in rodent models. Plantago major L. is a plant used traditionally for wound healing world-wide [13], and we have shown that isolated biologically active pectin polysaccharides from it have anti-infection effects in a mouse model for pneumococcal sepsis [14]. The medicinal Basidiomycetes mushroom Agaricus bM (Fig. 2) is a.k.a. A. brasiliensis because of its Brazilian origin, but has also been designated A. rufotegulis and A. subrufescens, already described in 1893 by CH Peck, [15]. It is closely related to the common champignon, A. bisporus, which has also been found to have beneficial health effects [16]. Since the mushroom was used in traditional medicine in Brazil against cancer, chronic hepatitis and other serious conditions, it was taken to Japan in the mid 1960-ties and cultivated commercially as health food. Scientists have since then documented immunomodulatory and antitumor effects of Agaricus bM in mouse models and we have found that an extract of it, Andosan™, that also contains two other related Basidiomycetes mushrooms from Japan, i.e. Hericium erinaceus and Grifola frondosa, can protect against both Gram positive and Gram negative coliform sepsis in mice [9,17]. This was basis for Dr. SV Bernardshaw’s PhD thesis in 2007 at the University of Oslo, Norway. Effect of Andosan was also examined against influenza infection in mice as well as against chronic hepatitis C virus infection in humans. Here, we review antimicrobial findings with bioactive polysaccharides such as β-glucans and Plantago major L. pectin and a combined extract of medicinal Basidiomycetes mushrooms in in vitro systems and in examples of infection models in the mouse.

**Fig. 1** Structure of two different types of β-1,3-glucan: Structural composition of SSG (scleroglucan) and MacroGard® showing the β-1,3-linked backbone and its β-1,6-attached side-chains, which are responsible for the binding to glucan receptors (CD11b/18, TLR2, dectin-1) and the resulting immunomodulatory effect. The figure, which also shows another SSG-like β-1,3-glucan, lentinan, is modified from an illustration in the publication: “MacroGard®: structural aspects and basic mode of action on phagocytes” from Biotec Pharmacon ASA, Tromsø, Norway by R.E. Engstad. Also see [6].

**Fig. 2** Agaricus blazei Murill. Photo NutriCon.
2. Infection models in which β-glucans and pectin have been used:

2.1. β-glucans and *M. tuberculosis* – infected macrophage cultures

Since β-glucans stimulate innate immune cells such as monocytes and macrophages via binding to TLR2 and other receptors, it was pertinent to examine whether these host cells for obligate intra-cellular pathogens such as mycobacteria, could be activated to intracellular killing of these parasites. We used both a highly virulent strain of *M. tuberculosis*, the culprit of the cardinal bacterial infection, tuberculosis, and its attenuated live vaccine; *M. bovis*, Bacillus Calmette-Guerin (BCG).

Peritoneal macrophages were harvested from Balb/c mice and cultured in vitro. The cells were then infected with the highly virulent *M. tuberculosis* strain H37Rv in presence or absence of PBS control, scleroglucan (SSG) or particulate yeast β-glucan MacroGard®(MG). After 24 h of co-incubation extracellular bacteria were washed away, the macrophages lysed and the lysate with the intracellular bacteria cultured for 3 weeks on Löwenstein-Jensen egg medium and examined by immunofluorescence microscopy after auramin O-staining of the acid-fast bacilli. Although SSG at 0.5 mg/ml gave a significant 40% reduction in the number of *M. tuberculosis* colony-forming units (CFU), particulate MG (but not soluble MG; not shown) was 50x more efficient at inhibiting *M. tuberculosis* growth dose-dependently (Fig. 3) [10].

![Fig. 3](image)

**Fig. 3** Effect on *M. tuberculosis* growth of yeast β-glucan (MacroGard® =MG) and scleroglucan (SSG) incubated simultaneously for 24 h with the tubercle bacteria in macrophage cell cultures, previously published [10].

2.2. β-glucan and *M. bovis*, BCG– infected Balb/c mice

Instead of hazardous animal studies with highly virulent *M. tuberculosis* bacteria, we chose to establish a model for *M. bovis*, BCG, in the susceptible Balb/c mice by i.v. injection of viable bacteria into the tail vein. The animals were injected i.v. either 100 µg of soluble β-glucan from barley (G-6513, from Sigma) or vehicle (PBS). At the peak of infection 4 weeks after challenge, the mice were sacrificed and major organs homogenized and cultured or stained for immunofluorescence microscopy. We found significantly lower bacterial counts in the spleen (p<0.01) of β-glucan-treated than of PBS-treated mice when given pre-challenge (Fig. 4). Similar findings were done in liver homogenates (not shown). When the β-glucan was injected post-challenge there was also a significantly lower bacterial load (p<0.05) in the spleen (Fig. 4), but not in the liver [11].
Fig. 4 Immunofluorescence microscopy of *M. bovis*, BCG, bacteria (formaldehyde-fixed and treated with auramin O) in spleen of Balb/c mice (n=8) sacrificed 4 weeks after challenge. Animals were given 100 µg of barley β-glucan i.v. 3 days pre- or 7 days post-challenge. P<0.05, **P<0.001. Adapted from figure in [11].

2.3. β-glucan and pneumococcal sepsis

NIH/OlaHsd mice infected i.p. with *S. pneumoniae* serotype 6B were also injected i.p. with SSG (4 µg (low dose)-200 µg (high dose)) or PBS either 3 days before or 3 h, 24 h and or 72 h after bacterial challenge. Tiny blood samples were collected daily from the lateral femoral vein and plated, and the number of bacteria (CFU) in the animals’ blood and their survival were recorded. Pre-challenge SSG administration protected against *S. pneumoniae* sepsis as shown by a dose-dependent inhibition of bacteremia and increased survival rates up to 50% with 200 µg of SSG as compared with 10% survival after 14 days of the PBS-treated mice (P=0.005) [8] (figs not shown). This high dose of SSG injected once post-challenge after 24 h had curative effect against *S. pneumoniae* 6B as demonstrated by 40% survival at end of experiment compared with none of the PBS controls (P=0.02) (Fig. 5).

Fig. 5 Survival (median values, n=8) from peritonitis and sepsis of NIH/OlaHsd mice challenged with *S. pneumoniae* serotype 6B and treated with PBS or SSG β-glucan (L=low and h= high dose) 3 h, 24 h and/or 72 h later (adapted from [8]).
2.4. Pectin: *Plantago major* L. pectin PMII and pneumococcal infection in mice

*Plantago major* L., large plantain leaves, have been used as a wound healing remedy in traditional medicine for centuries and in most parts of the World [13]. The purported wound healing effect is not well documented. Never-the-less, one might regard this plant as a potential source of immunomodulatory components triggering the healing process or other processes involving the innate immune system. This was supported by Lithander [18] who reported prophylactic effects of a *P. major* aqueous extract on mammary cancer in mice, indicating immunomodulatory activities. A complex pectin fraction, PMII, that was isolated from the leaves of *P. major* showed anti-complementary (complement-fixing) activity *in vitro* and was also shown to induce TNFα secretion after stimulation of human monocytes [19,20,21].

Pectin polysaccharides are water soluble compounds found in the cell wall of dicotyledons. In general, pectins are composed of unbranched homogalacturonan regions and regions with different types of side chains such as arabinogalactans, galactans or arabinans linked to rhamnogalacturonan sequences of the backbone in so called rhamnogalacturonan I (RGI) structures. In addition, single xylose residues and well defined side chains called rhamnogalacturonan II (RGII) are found linked to the galacturonan backbone. For review, see [22]. The fine structures of RGI vary with regard to monosaccharide composition, linkages, ramification and chain length. Structurally, PMII was composed of galacturonic acid (71.7 %), rhamnose (4.2%), arabinose (8.8 %), galactose (8 %) and glucose and had a molecular weight of 46-48 kDa. PMII was highly methylesterified (67 %), and contained both smooth and ramified regions. Structure-activity studies revealed that the RGI-like structures of PMII containing 1,4- and 1,3,6-linked galactose residues had the highest anti-complementary activity [23,20]. The fine structure and bioactivity of pectins from different sources vary. For instance, cabbage (*Brassica oleracea*) leaves, which are also used to aid the healing of wounds in folk medicine, were found to contain pectin fractions with lower complement-fixing activity than PMII [24] even when the same isolation procedure was applied. Multivariate statistical analysis suggested that pectin activity is enhanced by the content of 1,6- and 1,3,6- galactose side chains and low amounts of homogalacturonan regions [25]. It was also found that isolated single side chains of white cabbage pectin did not affect the complement system, side chains were only active when attached to the rhamnogalacturonan backbone [26]. The isolation procedure also affect the structure of isolated pectins as well as their activity [27]. Due to modest activity in the complement system, *Brassica* pectins were not subjected to further testing.

Due to its high complement-fixing activity, PMII was subjected to an *in vivo* study revealing a protective effect against bacterial infection in mice. Inbred NIH/OlaHsd and Fox Chase SCID mice were pretreated with i.p. 12, 120 or 1200 µg PMII, 1.2 µg LPS or PBS 3 days before infection with *S. pneumoniae* serotype 6B. In PBS treated mice, bacteremia levels increased after one day (see Fig. 6), and after 3 days none of the PBS treated mice were alive compared to ≥ 50 % in the PMII and LPS-treated groups. In PMII treated mice bacteremia rose moderately until reaching PBS levels at day 9, whereas bacteremia levels in LPS treated mice reached lethal levels after 4 days. PMII had no effect after established infection, and there was not found any correlation between levels of anti-6B pneumococcal IgM or IgG antibodies and the dose of PMII given indicating that the protective effect was due to stimulation of the innate rather than the adaptive immune system [14].
Colony-forming units (CFU) in peripheral blood from NIH/OlaHsd female mice pretreated with PBS, PMII low dose (PM L): 12 µg, median dose (PM m) 120 µg, high dose (PM h) 1200 µg or E.coli LPS (1.2 µg) i.p. 3 days before challenge with $10^6$ pneumococci 6B i.p. The data points represent median values from eight animals. Reprinted from [14] with permission from John Wiley & Sons, Inc.

3. Infection models in which Agaricus blazei extract has been used:

3.1. Antimicrobial effects of the Agaricus blazei Murill-based mushroom extract AndoSan™

The potential anti-bacterial effect of the Agaricus blazei Murill (AbM) (82%)-based Basidiomycetes mushroom extract, AndoSan™ (Immunopharma AS, Høvik, Norway), including Hericeum erinaceus (15%) and Grifola frondosa (3%), was studied in mice given monobacterial or fecal polymicrobial peritonitis. AndoSan™ was introduced by orogastric intubation to NIH/OlaHsd mice prior to (24 h or 2 h) or simultaneously with induction of peritonitis by intraperitoneal inoculation with moderately virulent S. pneumoniae serotype 6B [9]. End points were bacteremia and survival rate. Controls were mice treated likewise but given PBS instead of AbM. The number of CFU was significantly reduced in the AbM group compared to the PBS group (Fig. 7A). Furthermore, the effect was comparable and more pronounced when given 24 h before relative to 2 h before or simultaneously with the induction of pneumococcal peritonitis. The survival of the mice was improved in the three AbM treated groups of mice, but was also most pronounced (50%) after treatment of AbM 24 h prior to induction of peritonitis (Fig. 7B). Since cultivation of the bacteria in the presence of AbM on agar plates indicated no detectable reduction of number of CFU, AbM per se had no antimicrobial effect on the pneumococci. Increases in the level of pro-inflammatory cytokines MIP-2 (murine equivalent to human IL-8) and TNFα in the serum of mice receiving AbM once but more pronounced when received twice, indicated that the protective effect of AbM was mediated by involvement of the native immune system. In order to study further the potential protective effect of AbM in a more physiologically relevant setting for clinical and secondary aerobic peritonitis, an experimental and reproducible model for induction of fecal peritonitis was developed in Balb/c mice [17]. Dilutions 1/4, 1/8 and 1/12 of mouse feces inoculated i.p. in the mice lead to severe, moderate and mild peritonitis, respectively. In this model, using AbM compared with control (PBS) introduced orogastrically 24 h before bacterial inoculation, a significant protection was revealed as measured by significantly improved overall survival for all degrees of peritonitis (45% vs 28%) and particularly, severe peritonitis (25% vs 0%) (Fig. 8). Similarly, there was as significant reduction of CFU in AbM-treated mice with severe and moderate peritonitis [17]. The temperature measurements showed a negative correlation with the degrees of septicemia conditions and higher CFU, which is normal for septic mice. These animal experiments took place at The Norwegian Institute of Public Health, Oslo. Quantitative and qualitative characterization of the bacteremia revealed that both Gram-positive streptococci and Gram-negative...
coliorm bacteria dominated. In both studies the protective effect of AbM was demonstrated by use of two different strains of mice expressing either Th-1/Th-2 balanced immunity (NIH/OlaHsd) or pronation towards Th-2 immunity (Balb/c). A moderately virulent *S. pneumoniae* 6B [9] or fecal bacterial flora [17] were used in these studies. Since Andosan™ seems to inhibit TLR4 (the LPS receptor)-mediated cellular stimulation of NF-κB activation, this may partly explain the observed protection against Gram negative sepsis in the mouse model [12].

![Graph](image1)

**Fig. 7A** Number of CFU of *S. pneumoniae* serotype 6B in blood of NIH/OlaHsd mice after treatment intragastrically with AbM and PBS before (24 h) or simultaneously (0 h) with intraperitoneal bacterial inoculation (from [9] with permission).

![Graph](image2)

**Fig. 7B** Survival in NIH/OlaHsd mice given AbM or PBS intragastrically prior to (24 h) or simultaneously (0 h) with intraperitoneal inoculation with *S. pneumoniae* serotype 6B (from [9] with permission).
Fig. 8 Survival of severe fecal peritonitis in Balb/c mice after orogastric introduction of Andosan (AbM) or PBS control 24 h prior to challenge. The results are based on 2 separate experiments with 8 mice in each group (from [17] with permission).

Table 1 Comparison of minimum inhibiting concentration (MIC) of the polysaccharide and mushroom products reviewed.

<table>
<thead>
<tr>
<th>Polysaccharide or mushroom product</th>
<th>Antimicrobial action in type of infection model</th>
<th>MIC of compound given pre-challenge or with challenge*</th>
<th>MIC of compound given post-challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-glucan from barley (S-2721)</td>
<td>M. bovis, BCG-infection in mice</td>
<td>100 μg/ mouse (i.v.)</td>
<td>100 μg/ mouse (i.v.) N.D.</td>
</tr>
<tr>
<td>β-glucan from baker’s yeast</td>
<td></td>
<td>10 μg/ mouse (i.v.)</td>
<td></td>
</tr>
<tr>
<td>SSG</td>
<td>M. tuberculosis (strain H37Rv)-infected mouse macrophage cultures</td>
<td>500 μg/ml* in vitro</td>
<td>No effect N.D.</td>
</tr>
<tr>
<td>MacroGard® (particulate)</td>
<td></td>
<td>10 μg/ml*</td>
<td></td>
</tr>
<tr>
<td>MacroGard® (soluble)</td>
<td></td>
<td>No effect*</td>
<td>N.D.</td>
</tr>
<tr>
<td>SSG</td>
<td>S.pneumoniae (type 6B)-infection in mice</td>
<td>4 μg/ mouse (i.p.)</td>
<td>4 μg/ mouse (i.p.) (effect on bacteremia)</td>
</tr>
<tr>
<td>PMII</td>
<td></td>
<td>12 μg/ mouse (i.p.)</td>
<td>200 μg/ mouse (i.p.) (effect on survival)</td>
</tr>
<tr>
<td>AndoSan™</td>
<td>S.pneumoniae (type 6B)-infection in mice</td>
<td>0.9 μg/ mouse (p.o.), *also with challenge</td>
<td>N.D.</td>
</tr>
<tr>
<td></td>
<td>Fecal (Gram negative) bacteria-infection in mice</td>
<td>0.9 μg/ mouse (p.o.)</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

There was no direct antimicrobial effect of AndoSan™ against S. pneumoniae serotype 6B in bacterial cultures. Each mouse was given 200 μl of AndoSan™ by orogastric installation, which is equivalent to 0.9 μg according to the dry weight of 4.5 mg/ml after lyophilization of the extract (Samuelsen, unpublished results). The table shows that AndoSan™
was the product with the lowest MIC even though it was given enterally, in contrast with the parenteral administration of β-glucans and PMII. Hence, it proved to be the product with the highest efficacy in the comparison above.

3.2. Viral infections

Agaricus blazei extracts have previously been reported to inhibit certain viruses. More specifically, in vitro studies on cell cultures have found antiviral effects against Western equine encephalitis virus [28], poliovirus type 1 [29], and bovine herpes virus 1 [30]. As the extract has traditionally been used in connection with liver diseases, including chronic hepatitis, we were allowed to test the in vivo effect of AbM on five patients with chronic hepatitis C virus infection [31].

The patients did not respond to interferon treatment and were not given other anti-viral therapy. Daily, oral doses of AbM were administrated for one week. Blood samples were obtained before and after treatment. The viral load was slightly, but not significantly, decreased after treatment (5.3 compared to 5.8 million copies of virus per ml plasma). The experimental setup allowed us to examine changes in gene expression in leucocytes from the patients prior to and after treatment [30]. As might be expected, the changes were less pronounced compared to previous studies looking at similar effects on monocytes treated in vitro [32]. Moreover, the cytokine genes most strongly induced in vitro were not induced in vivo. The more notable changes in mRNA levels were related to genes involved in the G-protein coupled receptor signaling pathway, in cell cycling, and in transcriptional regulation. The results suggest that the β-glucans of the extract, which presumably are responsible for cytokine induction, did not readily enter the blood; while other components, such as substances proposed to have anticancer effects, were active. The treatment did, however, upregulate the gene for IFNα-receptor. Consequently, a study examining AbM intake combined with regular IFNα treatment, might have been of interest. However now, other antiviral treatment than IFNα is used against HCV infection.

The AbM extract was also tested on a mice model for influenza. No antiviral effect was demonstrated (unpublished results). The discrepancy between the previously published in vitro antiviral effects, and the in vivo results on hepatitis C and influenza virus, may be explained by the antiviral ingredients in the extract not readily entering the blood upon oral administration.

4. Conclusions

The time has come to exploit novel and alternative strategies to combat MDR resistant harmful and potentially lethal microbes. Since the mixed Basidiomycetes mushroom product AndoSan™ has proven to be the most efficient of the polysaccharide and mushroom-related products tested and reviewed here, we recommend this extract or components thereof for future investigative clinical studies in patients with hard-to-cure bacterial infections inflicted by MDR microbes. One such attempt is a planned clinical study, albeit awaiting ethical approval and financing, in which AndoSan™ can be used against MDR-tuberculosis in patients at Armauer Hansen Research Institute (AHRI) in Addis Abeba, Ethiopia. Regarding viral infections, we have so far not observed any significant effects of Basidiomycetes mushroom extracts on viral load.

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Conflict of interest GH is a stock holder of Immunopharma AS.

5. References


