

## REVIEW

# Can medicinal mushrooms have prophylactic or therapeutic effect against COVID-19 and its pneumonic superinfection and complicating inflammation?

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## Abstract

Medicinal mushrooms have documented effects against different diseases, including infections and inflammatory disorders. The related *Basidiomycota Agaricus blazei* Murill (AbM), *Hericium erinaceus* (HE), and *Grifola frondosa* (GF) have been shown to exert antimicrobial activity against viral agents, Gram-positive and Gram-negative bacteria, and parasites in vitro and in vivo. Since the mechanism is immunomodulatory and not antibiotoxic, the mushrooms should be active against multi-drug resistant microbes as well. Moreover, since these *Basidiomycota* also have anti-inflammatory properties, they may be suited for treatment of the severe lung inflammation that often follows COVID-19 infection. An AbM-based mushroom extract (Andosan™), also containing HE and GF, has been shown to significantly reduce bacteraemia and increase survival in mice with pneumococcal sepsis, and to improve symptoms and quality of life in IBD patients via an anti-inflammatory effect. Hence, such mushroom extracts could have prophylactic or therapeutic effect against the pneumonic superinfection and severe lung inflammation that often complicates COVID-19 infection. Here, we review antimicrobial and anti-inflammatory properties of AbM, HE and GF mushrooms, which could be used for the battle against COVID-19.

## 1 | INTRODUCTION

Edible mushrooms, especially of the *Basidiomycetes* family, have had a long and apparently successful medicinal use based on empiric observations, foremost in traditional Chinese and Japanese medicine. *Basidiomycetes* mushrooms such as *Agaricus blazei* Murill (AbM), *Ganoderma lucidum*, *Hericium erinaceus* (HE) and *Grifola frondosa* (GF) are consumed as immune response modifiers for prevention of cancer, or as nutritional support during chemotherapy, and

for chronic inflammatory conditions such as hepatitis and other diseases.<sup>1</sup> Substances derived from fungi include antibiotics, for example penicillin and griseofulvin, and the immunosuppressant, cyclosporine A, which is crucial in organ transplantation. Substances have been detected in higher *Basidiomycetes* mushrooms that have a range of therapeutic effects,<sup>2</sup> including chemically highly diversified anti-inflammatory compounds, such as polysaccharides,<sup>3</sup> terpenoids,<sup>4</sup> phenolic compounds,<sup>5</sup> glycerides<sup>6</sup> and other low molecular weight molecules.<sup>7</sup>

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Effects of AbM on infection, inflammation and tumour have been reviewed previously in SJI, including that of the AbM-based mycelium extract, Andosan™, which also contains HE (15%) and GF (3%).<sup>8</sup> It has been used in three placebo-controlled randomized clinical trials as supplement to regular treatment for inflammatory bowel disease (IBD); ulcerative colitis (UC) (50 patients) and Crohn's disease (CD) (50 patients),<sup>9-11</sup> multiple myeloma (MM)<sup>12</sup> (40 patients) and pollen allergy and asthma<sup>13</sup> (60 blood donors) without adverse effects. It reduced proinflammatory cytokines and improved symptoms and quality of life in IBD patients,<sup>9-11</sup> reduced allergy and asthma symptoms, specific IgE and basophil sensitivity in allergics,<sup>13</sup> and increased IL-1 receptor antagonist (IL-1ra), IL-7, T regulatory cells, dendritic cells (DCs) and expression of Ig, Killer Ig receptors (KIRs) and HLA genes in MM patients.<sup>12</sup> Moreover, since the beginning of this millennium there have been quite a few other reports on antimicrobial (Table 1, 2) and anti-inflammatory (Table 3) effects of medicinal mushrooms such as AbM, HE and GF.

The outbreak of a novel coronavirus (SARS-CoV-2) (COVID-19)-induced disease in China that causes serious respiratory illness, was declared a pandemic by the World Health Organization on 11 March 2020. Most of those who got sick from the infection, developed lymphopenia and pneumonia and in severe cases also high levels of proinflammatory cytokines.<sup>14</sup> This is similar to the 'cytokine storm' observed in SARS,<sup>15,16</sup> which gives rise to viraemia and inflammatory lung injury and may be followed by multi-organ failure and death. In some cases, this pathogenesis will be enhanced by secondary bacterial superinfection in the lung as well as development of septicemia. Immune dysregulation may play an important role in many viral diseases such as respiratory syncytial virus infection, where a disease-enhancing inflammation similar to the COVID-19 situation is dependent on the immune response in the airways mucosa.<sup>17</sup> In viral infections, Treg and Th17 cells have a complex interaction in which Tregs may inhibit immune activation and subsequent disease progression and maintain immune homeostasis, while Th17 cells will induce immune activation and propagate the inflammation.<sup>18</sup>

As the COVID-19 pathogenesis is unknown, similar to that of SARS, there are no approved drugs for the disease and vaccines are yet to be developed. Corticosteroids that otherwise are used for treatment of acute respiratory distress syndrome and severe lung injury,<sup>16</sup> strongly inhibit antiviral immunity and may be counter-indicated. An inhibition of a proximal immune response event such as activation of IFN-related pattern recognition receptors (PRRs) that are activated by pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) at the mucosa,<sup>19</sup> would seem unwise because of its general host defence regulatory function. Therefore, targets should be limited to proinflammatory and Th2 cytokines, such as oxygen radicals, TNF $\alpha$ , IL-1, IL-4, IL-6, IL-8 and IL-21 production.<sup>20</sup>

These, except for the IL-21 that has not been examined, are the very same effector arms that are counteracted by Andosan™ treatment.<sup>21-24</sup>

The aim of this article was to review possible effects that the much used and related medicinal mushrooms AbM, HE and GF might have against COVID-19 infection and its complications. Selection criteria were inclusion of PubMed/Medline indexed articles on antimicrobial and anti-inflammatory effects with these mushrooms.

## 2 | ANTIVIRAL EFFECTS OF ABM, HE AND GF

AbM has been shown to counteract the cytopathic effect induced by Western Equine Encephalitis (WEE) virus on VERO cells *in vitro*,<sup>25</sup> and in a plaque reduction assay with poliovirus to reduce the number of plaques suggestively by acting in the initial stage of viral replication (Table 1).<sup>26</sup> In patients with chronic hepatitis B virus (HBV) and C virus (HCV) infection, AbM extracts have been found to normalize liver function,<sup>27</sup> and to slightly decrease HCV plasma load.<sup>28</sup> Also antiviral effect of GF alone or combined with IFN $\alpha$  has been demonstrated against HBV in HepG2 cells, in which HBV DNA was inhibited.<sup>29</sup>

There are several reports regarding mushroom treatment of herpes virus 1 (HSV-1) and 2 (HSV-2): a protein isolated from GF inhibited HSV-1 replication *in vitro* and reduced severity of the viral infection upon topical administration in a mouse model.<sup>30</sup> Further, AbM polysaccharides inhibited HSV-1 infection in HEp-2 cell cultures.<sup>31,32</sup> Another AbM mycelium polysaccharide given orally to mice, reduced ocular, cutaneous and vaginal (HSV-2) infections by inhibition of virus attachment, entry and cell-to-cell spreading as shown by plaque reduction assay.<sup>33</sup> Suggestively, this occurred through interference with early events of viral penetration.<sup>31</sup> Yet, another GF polysaccharide was shown to block replication of enterovirus 71 (EV-71) - the major agent for foot, hand and mouth disease - suppress viral protein expression and exhibits apoptotic activity *in vitro*.<sup>34</sup>

With respect to influenza, one report found that AbM metabolites had direct antiviral effect against influenza virus among others *in vitro*,<sup>35</sup> and another reported inhibition by AbM extract against H1N1 influenza virus in a plaque formation test after the viral invasion of host cells.<sup>36</sup> Also, antiviral effects have been proved for HE: it was effective against intestinal damage of Muscovy duck reovirus in ducklings, in which injured mucosal immunity was restored.<sup>37</sup> Moreover, HE is reported to counteract Dengue virus infection *in vitro* as shown by inhibition of attachment and penetration in plaque reduction assays and reduction in viral gene expression.<sup>38</sup>

**TABLE 1** Antiviral effects of AbM, HE and GF (Human studies)

Viral agent	Experimental model	Mushroom product	Antiviral effect/Mechanism	Author	References
WEE virus	In vitro, cell cultures	AbM extract	Anti-cytopathic effect induced by WEE virus in Vero cells	Sorimachi et al, 2001	[25]
Polio virus	In vitro	AbM extract	Reduced virus replication	Faccin et al, 2007	[26]
HBV	HEp G2 cells	GF extract	Induction of endogenous antioxidant enzyme	Gu et al, 2006	[29]
	Patients with chron. Infection (n = 4)	AbM extract	Normalized liver function	Hsu et al, 2008	[27]
HCV	Patients with chron. Infection (n = 5)	Mycelium extract incl. HE, GF, (Andosan) p.o.	Slight reduction (not significant)	Grinde et al, 2006	[28]
HSV-1 or HSV-2	In vitro, and in Mice	GF protein, topical admin.	Reduced virus production	Gu et al, 2007	[30]
	HEp-2 cultures	AbM polysaccharide and beta-glucan	Inhibition	Minari et al, 2011	[31]
	HEp-2 cultures	AbM polysaccharide	Inhibition	Yamamoto et al, 2013	[32]
	Mice, ocular, cutaneous and vaginal infections	AbM mycelial polysacc., p.o.	Reduced topical infections	Cardozo et al, 2013	[33]
Influenza virus	In vitro	AbM metabolites	Direct antiviral action	Avtomomova et al, 2014	[35]
	Plaque formation inhib. test	AbM extract	Inhibition	Eguchi et al, 2017	[36]
Enterovirus 71	In vitro	GF polysaccharide, p.o.	Blocked viral replication	Zhao et al, 2016	[34]
Muscovy duck reovirus	Ducklings	HE polysaccharide	Restor. of injured mucosal immunity	Wu et al, 2018	[37]
Dengue virus	In vitro	HE	Inhibition	Ellan et al, 2019	[38]

### 3 | ANTIMICROBIAL EFFECTS OF ABM, HE AND GF AGAINST BACTERIA AND PARASITES

There are several publications regarding antibacterial and antiparasitic properties of AbM (Table 2). We reported 15 years ago that the AbM-based extract, Andosan™, when given orally 1 day before or at time of intraperitoneal (i.p.) inoculation of bacteria, significantly reduced bacteraemia and increased the animals' survival in two lethal bacterial sepsis models in mice.<sup>39,40</sup> One model was with Gram-positive pneumococci (*Streptococcus pneumonia* serotype 6B)<sup>39</sup> that tend to give pneumonia as superinfection in elderly COVID-19 infected patients.<sup>41</sup> The other sepsis model was with a suspension of air-exposed mouse fecalia, predominantly containing Gram-negative bacteria<sup>40</sup> and their toxins, which are feared culprits for sepsis development with its life-threatening complications from organ failure.<sup>42</sup> In the pneumococcal infection model, also effects of other Japanese AbM extracts were studied in a blinded fashion after administration orally 2h before i.p. bacterial challenge. However, only Andosan™ gave a statistically significant ( $P < .05$ ) decrease in bacteraemia (>1 log, day 10) and increase in survival rate; 38% (3/8) survival

day 6 in Andosan™ group and none day 5 in saline controls (Figure 1).<sup>8</sup> In fact, whereas 50% or 40% of the mice survived when given Andosan™ by gavage 24 hours before or at time of i.p. injection of the bacteria, respectively, only 13% of the saline gavage controls survived the 10 days of experimentation in follow-up experiments.<sup>39</sup> In the more lethal faecal sepsis model, 33% of mice given Andosan™ 24 hours prior to i.p. bacterial challenge survived during the 7 days experiment in contrast to the saline controls that were all dead on day 3.<sup>40</sup>

When testing natural products against synthesis of the bacteriocin mutacin by *Streptococcus mutans* in dental plaque biofilm, it was found to be inhibited by erinacine C from HE.<sup>43</sup> Quorum sensing plays an important role for virulence, biofilm formation and survival of many pathogenic bacteria, including Gram-negative *Pseudomonas aeruginosa*.<sup>44</sup> Interestingly, an AbM extract has been shown to have anti-quorum sensing effect as demonstrated by reduction of virulence factors of *P aeruginosa* and its biofilm forming capability, which may be used as weapon against such pathogens.<sup>44</sup> With regard to parasitic infections, AbM has been shown to counteract murine visceral leishmaniasis<sup>45</sup> by induction of a Th1 immune response,<sup>46</sup> and also to improve the consequence of cerebral malaria, by reduction of

**TABLE 2** Antimicrobial effects of AbM, HE and GF against bacteria and parasites

Microbe	Experimental model	Mushroom product	Antimicrobial effect/Mechanism	Author	References
<i>Streptococcus pneumoniae</i> serotype 6	Mice, sepsis	Mycelium extract incl. HE, GF (Andosan) p.o.	Reduced bacteraemia, Increased survival	Bernardshaw et al, 2005	[39]
<i>Streptococcus mutans</i>	In vitro	Erinacine from HE	Suppressed mutacin synthesis	Premnath et al, 2018	[43]
Faecal Gram neg. bacteria	Mice, sepsis	Mycelium extract incl. HE, GF, (Andosan), p.o.	Reduced bacteraemia, Increased survival	Bernardshaw et al, 2006	[40]
<i>Pseudomonas aeruginosa</i>	In vitro	AbM	Antiquorum sensing	Sokovic et al, 2014	[44]
<i>Pseudomonas</i> sp, pathogen opportunists	Plaque formation inhib. test	GF furanone	Inhibition	He et al, 2016	[48]
<i>Helicobacter pylori</i>	In vitro	HE extract	Inhibition	Liu et al, 2016	[49]
	In vitro & Mouse colonization assay	HE extract	Inhibition	Wang et al, 2019	[51]
Microbiota	Mice	HE	Improved colonic health	Wang et al, 2018	[52]
<i>Leishmania</i>	Mice, visceral L	AbM extract	Th1 response	Valadares et al, 2012	[45]
	Mice	AbM extract	Th1 response	de Jesus Pereira et al, 2015	[46]
<i>Plasmodium berghei</i>	Mice, cerebral malaria	AbM	Improved outcome	Val et al, 2015	[47]

*Plasmodium berghei* fluorescence labelled red blood cells in blood of mice, following their i.p. instillation.<sup>47</sup>

A GF furanone is found to inhibit opportunistic *Pseudomonas* sp. pathogens in a plaque formation test.<sup>48</sup> There are two reports on inhibitory effect of HE extract against *Helicobacter pylori* in vitro.<sup>49,50</sup> HE also affected microbiota, which resulted in improved colonic health.<sup>44</sup>

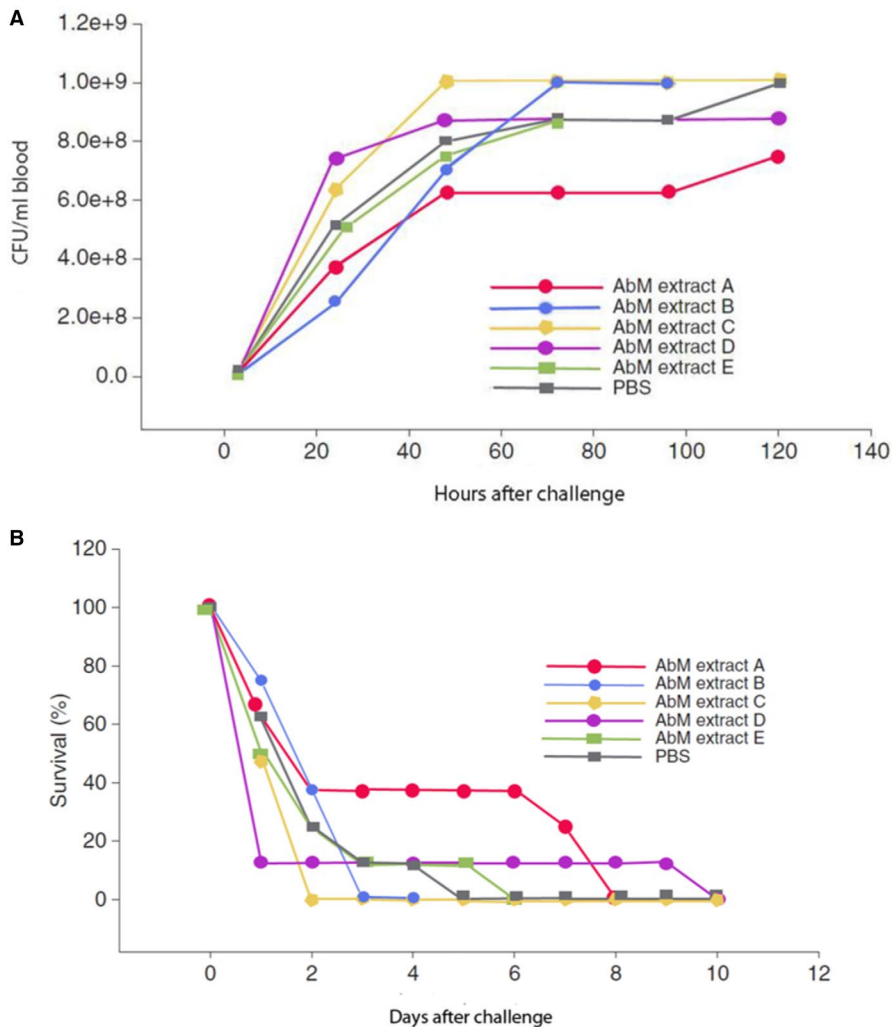
#### 4 | ANTI-INFLAMMATORY EFFECTS OF ABM, HE AND GF

Johnson et al reported that Andosan™ had predominantly anti-inflammatory effect in vivo, as demonstrated by systemic reduction in proinflammatory cytokines<sup>21</sup> and anti-oxidant effect in peripheral leucocytes (Table 3).<sup>24</sup> Another AbM extract given orally to rats with carcinogen-induced lung damage, attenuated the pulmonary inflammation and ensuing gross pulmonary consolidation.<sup>52</sup> As mentioned, AbM did improve cerebral inflammation from malaria.<sup>47</sup> Moreover, HE mycelium and HE-derived erinacine A protected against neural cell death induced by brain ischaemia in a rat model by inhibiting iNOS and MAP kinase, proinflammatory cytokines TNF $\alpha$ , IL-1 $\beta$  and IL-6, and promoting nerve growth properties.<sup>53</sup>

In a randomized clinical study (RCT), multiple myeloma patients undergoing high-dose chemotherapy and given add-on placebo-controlled treatment with the AbM-based Andosan™ for 2 months, were found to have the following immunomodulatory effects<sup>12</sup>: Reduced IL-1ra levels in plasma and increased T regulatory cells indicating anti-inflammatory effect, and increased plasmacytoid DC in blood and increased expression of genes in bone marrow aspirate at end of study vs before for KIRs and MHC antigens, the latter being important for antigen presentation. In another placebo-controlled RCT with IBD patients,<sup>9,10</sup> Therkelsen et al showed that Andosan™ given orally for 3 weeks reduced symptoms and increased quality of life especially of the patients with ulcerative colitis,<sup>9</sup> by an anti-inflammatory mechanism.<sup>13</sup> In a rat IBD model, also HE extract and isolated polysaccharide were shown to improve IBD-induced colonic mucosa damage by reducing MPO activity.<sup>54</sup> In colonic mucosa, also NF $\kappa$ B and TNF $\alpha$  expression was decreased and T cells were activated and growth of beneficial gut bacteria was promoted.<sup>54</sup> Additionally, a HE polysaccharide was shown to attenuate colitis in mice by reversing gut dysbiosis from potentially proinflammatory microbes, for example *Corynebacterium* and *Staphylococcus*, to potentially anti-inflammatory microbes, for example *Bacteroides* and *Bifidobacterium*.<sup>55</sup>

**TABLE 3** Anti-inflammatory effects of AbM, HE and GF (**Human studies**)

Product, Applic.	Study in, of	Effects	Mechanism	Author, Year	References
Mycelium extract incl. HE, GF, (Andosan) p.o.	Healthy Volunteers (n = 10)	Predominantly anti-inflammatory effect	↓ Proinflammatory cytokines	Johnson et al, 2009	[21]
Mycelium extract incl. HE, GF, (Andosan) p.o.	Healthy Volunteers (n = 8)	Antioxidant effect	↓ iROS prod. & adhesion molec. expressio in MΦ & granulocytes	Johnson et al, 2012	[24]
Mycelium extract incl. HE, GF, (Andosan) p.o.	IBD patients (50 UC & 50 CD)	Improved symptoms & QoL, espec. in UC	↓ Proinflammatory effect	Therkelsen et al, 2016a-c	[9-11]
AbM extract, p.o.	Rats, Pulmonary inflammation	↓ Lung damage induced by carcinogen	Attenuation of pulmonary inflammation & gross consolidation	Croccia et al, 2013	[52]
HE mycelium & erinacine A, p.o.	Rats, brain ischaemia	Protection against brain ischaemia injury induced neuronal cell death	Inhibition of iNOS/P3 MAPK Reduced IL-1β, IL-6, TNFα, nerve growth properties	Lee et al, 2014	[53]
AbM extract fractions	Mice, cerebral malaria	Improved consequence of cerebral malaria	↓ TNFα, IL-6, IL-1β Antimalarial activity	Val et al, 2015	[47]
HE extract & polysacc., p.o.	Rats, IBD	Improved damages in colonic mucosa of induced IBD	↓ MPO activ., NFκB, TNFα, ↑ T cell activ. Growth of beneficial gut bacteria and improved host immunity	Diling et al, 2017	[54]
HE polysaccharide, p.o.	Mice, Colitis	Attenuation of colitis, reversing of gut dysbiosis	Downregulation of oxidative stress & inflamm.-related signalling pathways, Maintaining intestinal barrier	Ren et al, 2018	[55]
AbM dry feed, p.o.	Mice, non-alcoholic steato-hepatitis	Prevention	Prevention of oxidative stress	Nakamura et al, 2019	[56]
Erinacine A-enriched HE mycelia, p.o.	Aged Mice	Increased longevity	Induction of endogenous antioxidant enzymes	Li et al, 2019	[58]



**FIGURE 1** Bacteraemia (A) (no. of CFU after plating of 25ul blood drawn daily from the animals' lateral femoral vein) and survival (B) of mice (8 per group) challenged i.p with *Streptococcus pneumoniae* serotype 6B 2h after oral administration (gavage) of different AbM extracts. Extract A is Andosan™, which was the only extract that showed significant differences ( $P < .05$ ) compared with saline control. Control was phosphate-buffered saline (PBS) (Modified from Ref. [4] with permission from Scand J Immunol for republication)

The mechanism was downregulation of oxidative stress and inflammatory signalling pathways and maintenance of the intestinal barrier by blocking phosphorylation of NF $\kappa$ B, and protein kinases MAPK and Act in mice with induced colitis.<sup>55</sup>

Moreover, AbM dry feed has been shown to prevent non-alcoholic steato-hepatitis (NASH) in a mouse model by preventing oxidative stress.<sup>56</sup> Similarly, a GF polysaccharide was shown to ameliorate lipid metabolic disorders in rats by beneficial regulation of microbiota.<sup>57</sup> Interestingly and in line with this, it was found that erinacine A-enriched HE mycelia given orally to aged mice, increased their longevity by induction of endogenous antioxidant enzymes.<sup>58</sup>

## 5 | MECHANISM OF ACTION— IMMUNOMODULATION AND DEFENCE AT THE MUCOSA

Immunomodulating  $\beta$ -glucans constitute the main part of the cell wall in fungi, including AbM, HE and GF mushrooms.<sup>59</sup>

Such polysaccharides have been found to have anticancer and anti-infection effects when given i.p. in mouse models.<sup>59-61</sup> Previously, we have also shown that yeast  $\beta$ -glucan given orally can protect against systemic *S. pneumoniae* infection in mice.<sup>62</sup> Moreover, owing to AbM-induced humoral and cellular responses, they are capable of adjuvating positive effects of hepatitis B virus and foot-and-mouth disease DNA vaccines in mice.<sup>63,64</sup>

AbM, HE and GF share PAMPs and DAMPs with other highly poisonous and health-threatening fungi and macrofungi. Accordingly, this must be the reason for the observed strong and rapid engagement of innate immunity and subsequent skewing of adaptive immunity from Th2 towards Th1 responses in the host when encountering edible and harmless mushrooms such as AbM, HE and GF.<sup>22,45,47,65</sup> PRR of the innate immune system such as TLR2, dectin-1 and CR3,<sup>66-68</sup> recognize immediately PAMP such as  $\beta$ -glucans from the main cell wall in mushrooms and fungi. TLRs and nucleotide-binding oligomerization domain (NOD)-like receptors are the two main PRR, which interact, for example in *Aspergillus fumigatus* infection.<sup>69</sup> Furthermore,  $\beta$ -glucan

activation of dendritic cells to IL-1 $\beta$  production occurs subsequent to NOD inflammasome activation.<sup>70</sup>

*Candida albicans* exists as a benign, commensal member of microbiota on mucosal surfaces in most humans, where it triggers numerous innate responses, but overgrowth can give localized mucosal or systemic infection.<sup>19</sup> Interestingly, *C. albicans* hyphae of the mycelium evoke PRR activation by their DAMPs and stimulate production of antimicrobial peptides<sup>19</sup> by epithelial and innate immune cells,<sup>71,72</sup> whereof defensins are the largest group.<sup>73</sup> Other properties than just their  $\beta$ -glucans probably are important triggers of defensins and other antimicrobial peptides. In fact, it was a surprise when it recently was revealed that the  $\beta$ -glucan content of Andosan<sup>TM</sup> was very low, probably due to its source being mycelia and not fruiting body.<sup>74</sup> Nevertheless, this mixed mushroom extract did stimulate TLR2 in monocytic cells.<sup>75</sup> Such AbM stimulation is shown to promote differentiation of M2 to M1 cells and induce a potent antitumour effect.<sup>76</sup> AbM also stimulates the expression of NKG2D/NCR cell surface receptors on NK cells.<sup>77</sup>

Since port of entry for most non-vector-borne viruses is the mucosa, which also is the body surface exposed to the mushroom extracts upon intake, *in vitro* virus studies referred to (see Table 1) are quite similar to the *in vivo* situation. Hence, AbM and GF may very well have similar antiviral effect *in vivo* against polio virus and EV-71, respectively, as demonstrated *in vitro*.<sup>26,34</sup> Enteroviruses such as polio and EV-71 infect by the faecal-oral route and target gastrointestinal epithelium where they are detected and trigger innate immunity signalling, which they yet are masters in evading.<sup>78</sup> This deregulation of inflammatory responses that results in a cytokine storm may play a critical role in pathogenesis of EV-71 pulmonary oedema<sup>79</sup> and that of COVID-19 infection as well.<sup>15-17</sup> Hence, one may assume that AbM and GF also could counteract the COVID-19 inflammatory lung injury.

Regarding HSV-1 and HSV-2 infections the host fails in initiating an effective early innate antiviral response and DC function, which should be targets for prophylactic strategies for preventing infections with these viruses.<sup>80</sup> This may be the very same mechanism(s) as for the reported antiherpetic action of a GF protein and a AbM mycelial polysaccharide *in vivo*.<sup>30,33</sup> Moreover, the amelioration by AbM of the WEE virus-induced cytopathic effect demonstrated *in vitro*<sup>25</sup> may reflect the antiviral effect against flaviviruses such as dengue virus also shown for HE.<sup>39</sup> In Muscovy duck reovirus infection, there was a net loss of beneficial bacteria that produce short chain fatty acids (SCFA) and compensatory proliferation of pathogenic bacteria (Gram-negative *Enterobacteriaceae*). This disruption of intestinal microbiota then results in severe pathology of intestinal mucosa and acute diarrhoea.<sup>81</sup> The injured mucosa and its immunity could be restored by HE, which was effective against this viral disease in ducklings.<sup>37</sup> Furthermore, oral intake in mice of Andosan<sup>TM</sup> is shown to

promote growth of *Bacteroides*, potentially anti-inflammatory microbes,<sup>57</sup> and production of SCFA (commun. prof. T. Ogita, Shinshu Univ, Nagano, Japan). This is also supported by our previous finding in the Gram-negative faecal sepsis mouse model of significantly increased survival after oral treatment with Andosan<sup>TM</sup>.<sup>39</sup> Moreover, the antiviral effect of AbM on influenza virus<sup>35,36</sup> is interesting because influenza corona viruses can give similar lung problems as COVID-19.

Although there was only insignificant reduction of HCV load in a few patients with chronic HCV infection who ingested Andosan<sup>TM</sup> for a week, there was an increased expression in peripheral mononuclear leucocytes of genes related to G protein-R signalling, cell cycling and transcriptional regulation.<sup>28</sup> G protein-coupled receptors for chemotaxins such as IL-8 chemokine, leukotriene 4B, the complement activation product C5a and bacteria-derived formyl peptides are associated with inflammation and microbial defence.<sup>82</sup>

Since complement is involved in the pathogenesis of several of the diseases, due to self-attack or contribution to the overall pathology,<sup>83-85</sup> which the mushrooms contained in Andosan<sup>TM</sup> have proposed or documented health effects against, the mechanism of action of Andosan<sup>TM</sup> may very well be linked to complement activity. Examples of diseases with beneficial effect of these mushrooms are as follows: Alzheimer's disease,<sup>86</sup> IBD,<sup>9,10</sup> bacterial infections,<sup>39,40</sup> malaria,<sup>47</sup> and allergy and asthma.<sup>13</sup> This is supported by AbM's ability to activate the alternative pathway of complement.<sup>87</sup> Also, there is new evidence for intracellular complement—the complosome—that is thought to be involved in immune cell regulation and metabolism in T cells and monocytes.<sup>88</sup> This may further explain the involvement of complement in pathogenesis of such quite different diseases. The existence of intracellular complement was detected more than 30 years ago by the first and second authors of this paper who showed that mononuclear phagocytes could produce all components for a functional complement system.<sup>89,90</sup>

## 6 | ABM, HE, GF AND COVID-19 INFECTION

In the current situation with a seemingly non-curable pandemic at hand and where candidate drugs and vaccines just are in the testing stage, one must look at alternative prophylactic and therapeutic principles. One candidate is immune prophylaxis and/ or therapy by use of immunomodulatory mushrooms. The *Agaricomycota* among the *Bacidiomycetes* mushrooms, AbM, HE and GF, are well-known medicinal mushrooms that have been used worldwide for a range of diseases in traditional medicine. In fact, many of those applications have been confirmed in preclinical and clinical studies. Focus has especially been on antitumour effects where cytotoxicity and apoptotic

mechanism have been revealed. However, in addition to an anti-inflammatory property, the mushrooms have also been found to induce enhanced Th1 cellular immune response, as demonstrated by increase in IFN $\gamma$ , IL-2 and IL-12 cytokines.<sup>22,65,91</sup>

Cells participating in the Th1 response are activated NK cells and cytotoxic Th1 cells and  $\gamma/\delta$  T cells, which besides tumour attack, also destroy virus-infected cells. Moreover,  $\gamma/\delta$  T cells play an important role in bridging the gap between innate and adaptive immunity, for example by being able to present antigen to conventional T cells, and they are predominantly localized in mucosa and epithelial sites,<sup>92</sup> which are entry points for viruses. Type III interferons (IFN- $\lambda$ ) are thought to be especially important in antiviral immunity.<sup>93,94</sup> Hence, the induction of the Th1 response by medicinal mushrooms could be tested as a novel modality for prophylactic and/or therapeutic measures against COVID-19 infection, as well as against its hazardous bacterial superinfection. In fact, bacterial infection, and especially with *S. pneumonia*, is found in 43% of the admitted elderly COVID patients and in 82% of the dead.<sup>41</sup> Besides elderly patients, also those with complicating underlying diseases such as chronic obstructive lung disease, cardiac diseases, diabetes and other chronic diseases with systemic affection<sup>95</sup> are at risk.

In pneumococcal sepsis in mice caused by the strain *S. pneumonia* serotype 6B, initially isolated from a patient, the disease could be counteracted by Andosan<sup>TM</sup> both when given orally either before or simultaneously with i.p. challenge with the pneumococci.<sup>39</sup> Hence, the extract seems to have both a prophylactic and a therapeutic effect against pneumococcal disease. Moreover, since the effect of Andosan<sup>TM</sup> was not antibiotoxic but immunomodulatory, this mushroom extract should be as effective against antibiotoxic-resistant bacteria as against antibiotoxic-sensitive bacteria. This aspect is especially interesting in context with the grave COVID-19 situation that has been experienced in Northern Italy and Spain, where pneumonia superinfection with multi-resistant bacteria may be an additive cause of death. Also, a more effective riddance of a bacterial superinfection would dampen the immune response and the ensuing inflammation that otherwise may complicate the COVID-19 disease. Non-digestible carbohydrates with prebiotic effect, such as  $\beta$ -glucan polysaccharides from medicinal mushrooms, stimulate growth of gut microbes that are favourable to the host's health, and spur on the production of SCFA, which energize anaerobic gut microbes, suppress pathogens (eg *Salmonella* sp.) and improve host immunity.<sup>95,96</sup> In this context, the increased production observed of SCFA by microbiota would probably stabilize colonocytes by being their main nutritional substrate, especially  $\beta$ -OH-butyrate (70%), generally as well as in IBD. Such

a trophical effect per se would normalize and equalize the physiological reaction to the body as such, which would benefit both healthy individuals prophylactically and patients therapeutically in the struggle against pathological agents, for example viral attacks such as from COVID-19.

Besides in the bacterial sepsis models,<sup>39,40</sup> the mushroom mixed product Andosan<sup>TM</sup> has also given positive results both in murine models for allergy<sup>22</sup> and colorectal cancer,<sup>91</sup> where an increased T helper cell (Th) 1 immune response was found in both models in addition to a proinflammatory response (increased IL-1 $\beta$ , MCP-1, TNF $\alpha$ ) in the latter. The proinflammatory response in mice is probably due to uptake of  $\beta$ -glucans from the murine gut as opposed to the anti-inflammatory effect in humans where  $\beta$ -glucan is hardly taken up or to a lower degree,<sup>97</sup> but may stimulate Peyer's patches in the gut-associated lymphoid tissue (GALT).<sup>98</sup> Therefore, other absorbable less defined low molecular weight substances (eg flavonoids) with anti-inflammatory and/or antioxidant activity probably contribute to this effect. In addition, in a placebo-controlled RCT in individuals with pollen allergy and asthma, Andosan<sup>TM</sup> supplementation before the pollen season resulted in decreased symptoms, medication, specific plasma IgE levels and basophil sensitivity, owing to a skewing of Th1/Th2 cells towards the Th1 phenotype.<sup>13</sup> The Th1 response is besides its induction of antitumoral and anti-allergic activity, also driving an antiviral immune response as discussed.

In conclusion, from the literature it seems possible that the related medicinal *Basidiomycetes* mushrooms, AbM, HE and GF would have merit as prophylactic or therapeutic add-on remedies in COVID-19 infection, especially as countermeasures against a pneumococcal superinfection, even when caused by multi-resistant bacteria, as well as for the immune overreaction and damaging inflammation that occurs with COVID-19 attack.

## CONFLICT OF INTERESTS

Geir Hetland is a cofounder and shareholder of Immunopharma, Oslo, Norway. The other authors declare no commercial or financial conflict of interest. Immunopharma had no other role than providing Andosan<sup>TM</sup> free of charge for the studies referred to.

## AUTHOR CONTRIBUTIONS

Geir Hetland wrote the manuscript, and Egil Johnson, Soosai Pillai Bernardshaw and Bjørn Grinde revised the manuscript. All authors have previously been much involved in several of the articles that this review is built upon.

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