Preventive Effect of Food Mushrooms Against Herpetic or SARS-Cov-2 Infections

(Running title: Effect of mushrooms against viral infections)

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Abstract

Background: Some mushrooms possess strong immunostimulating properties and may prevent the occurrence of viral infections.

Objective: Assess whether oral intake of food mushrooms may decrease the incidence of herpetic or SARS-COV-2 infections.

Methods: Descriptive retrospective epidemiological study with data collected during routine gastroenterological consultations in patients with a high risk of viral infections and who are recommended to take mushrooms. Compliant and non-compliant groups are compared.

Results: 186 patients are included. 156 patients are compliant. The long-term intake of Coriolus versicolor, Phellinus linteus, Grifola Frondosa or Ganoderma lucidum significantly decreases the global risk of viral infection (89.4% versus 13.3%; p<0.001). More specifically, this intake decreases the risk of COVID-19 (7.7% versus 13.4%; p<0.001), herpetic flares (3.2% versus 39.1%; p<0.01) and of polyps or HPV-induced lesions (0.7% versus 6.7%; p<0.001). These mushrooms also improve gastroduodenal voiding and jejunal motility.

Conclusion: Food mushrooms may decrease the risk of viral infections and improve the voiding of the foregut.

Keywords: Mushroom- herpes- COVID-19

List of abbreviations:

- BMI: Body Mass Index
- Crohn: Crohn’s disease
- CMV: Cytomegalovirus
- COVID-19: Coronavirus Disease
- CPGG: Coriolus versicolor, Phellinus linteus, Grifola frondosa and Ganoderma lucidum
- EBV: Epstein-Barr virus
- E-VOCs: Exhaled Volatile Organic Compounds
- H2: hydrogen
- H2S: hydrogen sulphide
- HIV: Human immunodeficiency virus
- HPV: Human papillomavirus
- HSV-1: Herpes virus type 1
- IFN: interferon
- LMW-HA: Low molecular weight hyaluronic acid
- SIBO: Small Intestinal Bowel Overgrowth
- UC: Ulcerative Colitis.

Introduction

SARS-CoV-2 may infect and multiply in the lung and in the bowel [1]. Bowel involvement may precede lung infection, especially when interferons and CD8+ responses are defective [2, 3]. Coronavirus disease-19 (COVID-19) has therefore been associated with dysbiosis [4-9] and with specific exhaled-volatile organic compounds (E-VOCs) in breath [10]. Treatment of dysbiosis or at least improvement of intestinal flora could become a strategy to prevent severe COVID-19 infection [11].

Altered flora is frequently associated with inadequate gastroduodenal voiding [12]. Furthermore, Herpes simplex virus type 1 (HSV-1) [13-15] or Cytomegalovirus (CMV) [16-19] has been implicated in gastroparesis in immunocompromised or non-immunocompromised patients.

Food mushrooms are well known immunostimulating agents [20, 21]. Since they are not extracts and since the recommended amount of product is small, they can be...
Patients should provide with a full medical history, especially regarding COVID-19, herpes simplex, herpes zoster, periodontitis, cancer or precancerous lesions including HPV-induced cervix lesions, repeated respiratory tract infections, CMV IgG+, hypogammaglobulinemia, chronic non-specific lymphadenopathy, Human Herpes Virus type-6-induced infection, medical history of clinical Epstein-Barr virus (EBV) mononucleosis or hepatitis A, or EBV-reactivation.

At inclusion, the patients present at least with two of the above-mentioned signs of immunosuppression within the five previous years.

CMV serology, serum Low-Molecular-Weight-Hyaluronic acid (LMW-HA) levels, and transabdominal plus thyroid ultrasound examinations are routinely performed in patients consulting for SIBO.

Patients underwent a breath test after a fasting period of at least 12 hours. All patients should have discontinued antibiotic therapy for at least 3 weeks before coming to the consultation for SIBO in order to avoid altered digestive flora. Detailed results of gas measurement are not provided in the study since SIBO is not targeted. Only fasting levels of hydrogen (H2) will be provided.

Patients signed a written consent for the possible retrospective use of the epidemiological collected data.

**Exclusion criteria:** Uncontrolled Crohn, ulcerative colitis, auto-immune hepatitis, rheumatoid arthritis, multiple sclerosis, sarcoidosis, endocrine disease (including thyroid insufficiency or diabetes mellitus), mastocytosis or mast cell activation syndrome, anorexia, pancreatitis or HIV infection.

Lack of CMV serology analysis, transabdominal ultrasound, signed consent for possible retrospective epidemiological use of data. Recent or repeated massive destruction of the digestive flora by antibiotic therapy or oral intake of essential oils leading to and less than 2 ppm of VOCs at the first measure, after 10 hours of fasting. Incomplete data on drug or food complement intake.

**COVID-19**

The diagnosis of COVID-19 was usually made by PCR and reported by the patient him or herself or written on his/her hospital record. It could also have been made by the general practitioner after suggestive symptoms and a serological control. They all have recovered (except one patient with asthenia) at least one month before the consultation.

**Ultrasound**

Gastroparesis was diagnosed when the surface of the stomach reached 10 cm². Ileal distension was diagnosed as soon as ileal diameter reached 2.2 cm at the ileocecal junction. Lack of gastroduodenal voiding was diagnosed when no evacuation of bubbles between the superior mesenteric artery and the aorta was observed after 2 minutes of osteopathic abdominal manoeuvres. Jejunal hypotonia could also be implicated. In that case, the jejunum contains few bubbles and no peristalsis is
visualized [43, 44]. Abdominal ultrasound examination also enables to diagnose liver steatosis.

**Food mushrooms**

At least two types of organic mushrooms were recommended on a long-term basis: *Coriolus versicolor*, *Phellinus linteus*, *Grifola frondosa* or *Ganoderma lucidum*. The recommended dose was 200 mg twice a day for each mushrooms, in food or on the tongue.

**Control group**

All consulting patients were pre-included in the study and no case was discarded except when at least one exclusion criteria were identified. As a consequence, no recruitment or selection bias is expected. The compliant group and the non-compliant group are compared. The control group is the non-compliant group and appears appropriate.

**Efficacy**

The preventive therapy was considered to be efficacious when patients did not experience any episode of herpetic, HPV, SRAS-COV-2, or upper respiratory tract infection within the follow-up period. Of course, only compliant patients were considered.

**Compliance**

The compliance was evaluated by two methods. Firstly, the patient fills the Morisky’s questionnaire [39]. The compliance was assessed acceptable when the score exceeds “6”. Secondly, compliance was evaluated according to the copies of all ordering forms of CPGG. We requested at inclusion and we remind this requirement at the end of every following consultation that the patient should provide a copy of each ordering form to the clinical centre [40, 41].

**Statistics**

Comparisons of percentage used two-sample t-tests. Yates correction was used for small samples. Comparisons of means used a Student’s t-test. Compliant and non-compliant group were compared for all parameters. Because of the large number of tests necessary for this specific analysis the threshold of statistical significance was set to p<0.01.

**Results**

This descriptive epidemiological study includes 186 patients. At the first consultation, all patients present with an increased risk of viral infection according to the physician who therefore recommended organic immunostimulating mushrooms: CPGG. This preventive antiviral therapy was always initiated before the COVID-19 pandemic.

The mean number of signs of immunosuppression at the first consultation was 3.0 +/- 1.0 versus 3.8 +/- 1.3 (table 1). 156 patients were compliant. 30 patients did not follow the recommendations. The mean duration of therapy is equal to 2.6 years +/- 1.3 in the compliant group versus 2.2 years +/- 1.5 in the non-compliant group.

Concomitant alteration of the foregut motility is frequent: 79.5 versus 76.7% for gastroduodenal voiding and 71.2% versus 66.7% for jejunal hypotonia. Jejunal hypotonia was always associated with decreased mucosal thickness. The descriptive demographic data are summarized in table 1. The two groups were similar.

| Table 1: Descriptive data of the 186 including patients, according to observance (percentages or mean +/-standard deviation), at the first consultation. |
|-----------------|-----------------|-----------------|--------------|
| **Age (years)** | **Compliant group** | **Non-compliant group** | **P value** |
| 156 patients    | 55.2 +/- 12.9   | 51.1 +/- 14.1   | >0.05        |
| Female          | 82.1%           | 80%             | >0.05        |
| Body Mass Index (BMI) | 22.0 +/- 3.2    | 21.0 +/- 2.9    | >0.05        |
| Number of signs of immunosuppression | 3.0 +/- 1.0 | 3.8 +/- 1.3 | >0.05 |
| Herpetic flares | 65.4%           | 86.7%           | >0.05        |
| IgG CMV+        | 35.9%           | 46.7%           | >0.05        |
| HPV infection   | 21.8%           | 16.7%           | >0.05        |
| Periodontitis   | 57.7%           | 53.3%           | >0.05        |
| Cancer or precancerous lesion | 28.2% | 23.3% | >0.05 |
| Gastroduodenal voiding disturbance | 79.5% | 76.7% | >0.05 |
| Jejunal hypotonia* | 71.2% | 66.7% | >0.05 |
| LMW-HA (µmol/l) | 61.4 +/- 47.4   | 47.8 +/- 34.5   | >0.05        |
| CPGG recommended | 100%          | 100% (not taken) | NR          |

* always associated with decreased mucosal thickness
improved. The LMW-HA level decreased only in the compliant group (-5.6 +/- 4.0 versus 1.5 +/- 8.4; p<0.001).

The variation of H2 concentration in breath moderately increased in the compliant group (3.0 ppm +/- 2.9 versus -2.7 +/- 3.5; p<0.001), which suggests larger hydrolytic and glycolytic activities of the intestinal flora after CPGG actual intake (table 2).

<table>
<thead>
<tr>
<th>Compliant group 156 patients</th>
<th>Non-compliant group 30 patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global antiviral success rate</td>
<td>89.4%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Mild COVID-19</td>
<td>7.7%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Herpetic flares (recurrence)</td>
<td>3.2%</td>
<td>39.1%</td>
</tr>
<tr>
<td>Colonic polyps or HPV-induced lesions</td>
<td>0.7%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Improvement of gastroduodenal voiding</td>
<td>5.5%</td>
<td>-3.3% (worsening)</td>
</tr>
<tr>
<td>Improvement of jejunal hypotonia</td>
<td>25.7%</td>
<td>0</td>
</tr>
<tr>
<td>Variation of LMW-HA</td>
<td>-10.6 +/- 8.0</td>
<td>-0.2 +/- 2.1</td>
</tr>
<tr>
<td>Variation of H2 level in breath</td>
<td>3.0 ppm +/- 2.9</td>
<td>-2.7 ppm +/- 3.5</td>
</tr>
</tbody>
</table>

Table 2: Evaluation of the effect of CPGG according to observance (percentages or mean +/-standard deviation), at the end of the follow-up period.

Discussion

Antiviral and anticancer immunity

Antiviral immunity is mainly based on T cytotoxic cells and type I interferon (IFN) response [43], especially for chronic infections such as herpetic viruses (herpes simplex, herpes zoster, EBV, CMV) or HPV.

SARS-CoV-2

SARS-CoV-2 appears to be particularly sensible to type I IFN response [44, 45]. Inhibition of type I IFN, for example by auto-antibodies, predispose to life-threatening COVID-19 [46, 47]. Such auto-antibodies also predispose to HSV-1 infection [48-50]. CD8+ cytotoxic T lymphocytes and IFN-γ are essential for coronavirus clearance [51, 52].

Herpes simplex or CMV, and T cytotoxic cells/IFN type I

The activation and regulation of T cells play a crucial role in host-mediated immune involvement in clearing HSV-1 [53, 54]. Type I IFN dysregulation in response to HSV-1 infection may favour neurotoxicity [55, 56]. However, HSV-1 has evolved multiple strategies – especially on the type I IFN signal pathway or on autophagy - to evade host innate responses and facilitate its infection [57].

Human cytomegalovirus (HCMV) is a member of the β-herpesvirus family that occupies hosts for life despite a consistent multi-prolonged antiviral immune response. The type I IFN system represents a first line of host defence against CMV [58].

HPV and IFN

IFN-alpha has been shown to inhibit the development and progression of cervical cancer [59]. Recently, immunotherapy with interferon and dendritic cells has been used on intraepithelial and invasive cervical lesions with promising results [60]. A decreased production of some specific classes of IFN is associated with high-risk-type HPV lesions suggesting an important role of IFN in the pathogenesis of HPV lesions [61]. Please note the efficacy of Coriolus versicolor-based vaginal gel in women with cervical uterine high-risk HPV infection [62].

Cancer or precancerous lesions

IFNs play also a key role in anticancer immunity [63-65]. Cancerous patients are at increased risk to develop a COVID-19 infection [66]. The association between IFN, natural killer cell activity and the risk of colorectal neoplasia is well established [67-69].

We previously reported that patients with a medical history of herpetic flares or certain types of cancer or precancerous lesions (i.e. breast, colon and HPV-induced cancers) are at increased risk of COVID [10].

Patients enrolled into this epidemiological study were selected on clinical criteria which highly suggest a compromised antiviral or anticancer immunity. We therefore expected that products able to stimulate either T cytotoxic cells or IFN type I synthesis may decrease the risk of viral recurrence.

Stimulation of immunity by mushrooms

The immunostimulating antiviral and antitumoral effects of CPGG are well documented [20, 21, 27-37]. This retrospective epidemiological study confirms that long term intake of small amounts of CPGG may prevent the occurrence of herpetic and COVID infections. This study does not enable to discuss specific mecanisms, especially because repeated dosages of cytokines or of T cytotoxic cells are not available in routine clinical practice, especially on a long-term basis.

However, no case of cytokine burst was reported in this cohort although all received CPGG. This argument rather suggests that CPGG acts at least partially through other mechanisms than direct immunostimulation with strong cytokine release or strong T cytotoxic cells activation. Some other possible mechanisms are further discussed.
Regulation of inflammation or dysbiosis by CPGG

In a preliminary study, we reported that severe periodontitis is associated with an increased level of LMW-HA, and with an increased risk of adenocarcinoma [70]. LMW-HA is known to increase endothelial permeability, to stimulate receptors of cancer stem cells and to favour cancer cells metastasis. Migration of stem-cells according to LMW-HA gradient has been documented [71-74]. Although increased levels of LMW-HA have been reported in cervix ripening during premature labour [75], we did not find any association between increased LMW-HA levels and cervix dysplasia.

In this cohort, CPGG decreases levels of LMW-HA and may therefore abate chronic inflammation and tissue destruction. This effect can be explained by many mechanisms such as recovery or strengthening of mucosal integrity, decreased gut dysbiosis or immunomodulation.

Simultaneous recovery of jejunal mucosa, foregut motility, microbiota recovery (H2 increase), and decreased tissue destruction (LMW-HA levels decrease) suggest a multifactorial effect.

Association between gastroduodenal or jejunal motility and dysbiosis or visceral fat

This epidemiological study supports that immunosuppression is frequently associated with foregut dysmotility and jejunal mucosal atrophy.

Bacterial metabolic pathways are intricate. Reduction of sulphate into H2S requires H2 [76]. H2S enables NO synthesis [77]. H2S and NO are necessary for gastroduodenal voiding [12].

Altered gastroduodenal voiding is associated with increased LMW-HA levels, pancreatic steatosis and hyperglycaemia. However, it is not associated with herpetic flares, HPV-induced lesions or COVID-19 infection [12].

We therefore suggest that viral infections are not the direct cause of disturbed motility and altered mucosal wall. However, neuro-invasive viruses may benefit from pre-existing conditions (e.g. leaky gut syndrome, vagal impairment, decreased autophagy or chronic inflammation) to reach the autonomic nervous system and exacerbate gastroduodenal motility.

Link between viral infection and dysbiosis or altered foregut motility

SARS-COV-2 is known to be neuro-invasive and to induce neurological complications [78-80]. A specific cluster of E-VOCs (cluster S8 to 74.9s) produced by gut bacteria is associated with mild-COVID, herpetic infections, or cancer or precancerous lesions [10]. This cluster may be a marker of gut-TH1-immunosuppression which could favour the spread of SARS-COV-2 from the gut to the lung. This cluster is also associated with cancer and arrhythmia [81] and therefore rather appears to be at least partly related to tissue destruction and vagal imbalance.

Autonomic imbalance is expected to favour severe COVID-19 infections [82, 83]. Therefore, vagal stimulation is expected to decrease the spread of SARS-COV-2 through the gut the lung or to the central nervous system [84, 85].

Please note that Coriolus versicolor has been associated with cognitive function improvement in Alzheimer patients [86, 87] and with the recovery of jejunal mucosa after mycotoxin-induced atrophy [88]. The concomitant improvement of the foregut motility by CPGG might illustrate a partial recovery of jejunal atrophy and of vagal activity.

Autophagy

Inadequate autophagy is associated with neurodegenerative diseases and impairment of the autonomic nervous system [89-91].

HSV-1 limits autophagy which favours its spread [92-95]. In contrast, SARS-CoV-2 increases autophagy at its advantage [96-98]. Grifola frondosa, Phellinus linteus and Ganoderma lucidum trigger autophagy [99-101]. Coriolus versicolor stimulates TLR4 [102,103]. TLR4 stimulation may induce autophagy [104]. However, Coriolus versicolor is able to clear prion-infected cell without the involvement of autophagy [105]. Another cleaning mechanism, yet unknown, is therefore perhaps involved. Please note that autophagy regulates the diversity of microbiota as well as the host immune responses [106].

Regular intake of small amounts of food mushrooms and global health

An increased life-expectancy is associated with the regular intake of vegetables [107] or of mushrooms [108] especially in case of organic food consumption [109-111]. It is therefore not surprising to observe a decreased risk of viral infection with regular intake of organic CPMG. Such an effect could be attributed to compounds stimulating immunity or autophagy [112]. It may also be related to endobiote contained in organic food. Endobiote or their bacteriophages may colonize the mucosa and participate to the control of dysbiosis or inflammation [113-116].

We hypothesise that restored autophagy is the initial cornerstone of the protective effect and is afterwards associated with appropriate diversity of microbiota, vagal preservation and foregut motility, and eventually mucosal thickness and gut-immunity.

We then speculate that long term CPGG intake favours adequate autophagy. Further investigations are necessary to clarify the mechanisms of action of CPGG.

Limitations of the study

It is a retrospective epidemiological study with a large diversity of therapies and behaviours. However, the
population included was quite homogeneous because of restrictive inclusion and exclusion criteria. Compliant and non-compliant groups were similar regarding demographic data, BMI, digestive vagal alterations, or medical history of viral infection and there is no reason to suspect any interfering factor other than observance.

However, two biases can be evoked. Firstly, dissatisfaction may be correlated with lack of observance and may end to patients lost to follow-up. Since no side effects are associated with the intake of low amounts of mushroom, only dissatisfaction with effectiveness can be evoked. Such a bias will reduce the percentage of failure in the non-compliant group and will decrease the difference between the two groups.

Secondly, some patients of the non-compliant group may have partially taken CPGM. Such a situation will also decrease the difference between the two groups.

In both instances, the biases tend to misleadingly narrow the differences between the two groups. It therefore suggests an even stronger effect of CPGM and consequently does not invalidate the findings.

No cytokine dosage was performed to investigate immunostimulation. However, clinical parameters are stronger variables to assess efficacy in clinical practice – such as overall or disease-free survival in oncology. Nevertheless, this study cannot provide biological arguments on the mechanisms of the observed antiviral protection.

**Application of this new knowledge for routine practice**

Long term intake of small doses CPGG may participate to antiviral prevention. The mechanism of action probably implies the repair of an adequate mucosal barrier – associated with appropriate gastroduodenal and jejunal motility leading to permanent mucosal cleaning (appropriate autophagy) and microbiota diversity – rather than the release of cytokines.

We therefore recommend introducing long term small doses of CPGG and detecting its effect by breath test and transabdominal ultrasound examination.

Breath test may detect a slight increase in hydrogen concentration and ultrasound examination may detect improved motility of the foregut associated with mucosal repair. These signs will suggest the efficacy of CPGG and that the patients are better protected against several viral diseases, especially those which require a digestive phase with subsequent crossing of the mucosal wall.

**Conclusion**

Immunosuppressed patients appear to benefit from long term intake of small amount of CPMG, especially regarding herpetic or SARS-COV-2 infections.

The mechanisms of action are yet only hypothetical. However, improvements of the foregut motility and of the mucosal wall have been objectivised. An increase in microbial diversity is possible. A chronic high increase of cytokine levels is unlikely.

Further investigations are necessary to determine the role of autophagy and of the foregut microbiota diversity, as well as of the vagal nerve in the protection of the mucosa. However, since low amounts of CPGG are innocuous and inexpensive, we suggest recommending such a therapy in patients considered at risk to develop severe or recurrent viral infections.

We also suggest investigating systematically the foregut mucosal wall and its motility by a transabdominal examination.

**Acknowledgment(S) And Conflicts of Interest**

**No conflict of interest to disclose.**

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