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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

classified as spice or food. They are devoided of risk, except for Shiitake with may be associated with severe allergic reaction [22-27].

Coriolus versicolor, *Phellinus linteus*, *Grifola frondosa* and *Ganoderma lucidum* (CPGG) are well documented immunostimulant mushrooms and are therefore currently recommended in immunosuppressed patients to either treat cancer [27-30] or to prevent viral infections [31-37].

We wonder whether long term intake of small amounts of immunostimulating agents may prevent the occurrence of viral infections in immunocompromised patients. We investigated whether they may simultaneously improve gastroduodenal or jejunal motility, or microbiota diversity.

Compliance is a main stumbling-block in long term therapy, especially regarding prevention and without the sting of symptoms reduction. We therefore routinely measure compliance with the Morisky's questionnaire [38] and by controlling of the ordering forms [39, 40] of CPGG.

We identified patients followed for SIBO for at least one year, without ongoing inflammatory diseases – especially without auto-immune diseases - and with a previous medical history of repeated viral infections or of immunosuppression and who were recommended to take CPGG.

Abdominal ultrasound was performed to investigate gastric, jejunal and ileal movements [42,43]. The compliant and the non-compliant groups were compared.

Material and methods

This work is a descriptive retrospective epidemiological study.

Data were collected during the normal course of routine gastroenterological consultations for Small Intestinal Bowel Overgrowth (SIBO). The recruitment started on 2016 January 1st and the last follow-up consultation ended on 2021 February1st.

There was no hypothesis testing before data collection, no data collection beyond that which is part of routine clinical practice, no scheduled data analysis before the work has already been done. This retrospective analysis of Case Series cannot therefore be qualified as "research" and does not requires approval from ethics boards designed to protect humans involved in clinical research, according to the International Committee of Medical Journal Editors (ICMJE).

Inclusion criteria. Patients consulting for SIBO and who underwent a breath test

The first consultation was planned before the start of the COVID-19 pandemic in France: between 2016 January 1st and 2020 February 1st. The last follow-up consultation was planned on 2021 February 1st. The follow-up period lasts at least one year. Patients are followed every 6 months.

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*), mastocytose 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 cm^2. 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 manoeuvers. 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.

	Compliant group 156 patients	**Non-compliant group 30 patients**	**P value**
Age (years)	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

Table 1: Descriptive data of the 186 including patients, according to observance (percentages or mean +/-standard deviation), at the first consultation.

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. Regular intake of CPGG significantly decreases the risk of viral infection (89.4% versus 13.3%; $p<0.001$). Herpetic flares were divided by twelve (3.2% versus 39.1%; $p<0.01$). COVID-19 occurrence was almost lowered by 50% (7.7% versus 13.4%; $p<0.001$). Gastroduodenal voiding and jejunal tonicity were

improved. The LMW-HA level decreased only in the compliant group (-5.6 +/- 4.0 versus11.5 +/- 8.4; p<0.001).

The variation of H2 concentration in breath moderately increased with time 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).

	Compliant group 156 patients	Non-compliant group 30 patients	P value
Global antiviral success rate	89.4%	13.3%	<0.001
Mild COVID-19	7.7%	13.4%	<0.001
Herpetic flares (recurrence)	3.2%	39.1%	<0.001
Colonic polyps or HPV-induced lesions	0.7%	6.7%	<0.001
Improvement of gastroduodenal voiding	5.5%	-3.3% (worsening)	<0.001
Improvement of jejunal hypotonia	25.7%	0	<0.001
Variation of LMW-HA	-10.6 +/- 8.0	-0.2 +/- 2.1	<0.001
Variation of H2 level in breath	3.0 ppm +/- 2.9	-2.7 ppm +/- 3.5	<0.001

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 1 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 immunity involved 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 58 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 SRA-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, SRAS-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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