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Alternative Medicines for Encephalitis

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1. Introduction

Encephalitis can be caused by several viruses, including western equine encephalitis (WEE) virus, Japanese encephalitis virus, herpes simplex virus (HSV), human immunodeficiency virus (HIV), influenza viruses and the measles virus. Bacteria such as *Neisseria meningitidis* and *Treponema pallidum* have also been shown to be causative agents of encephalitis. There are no medications currently available that selectively target virus-infected cells, although some nucleotide derivatives, and oseltamivir, are exceptionally effective against herpes simplex and influenza viruses, respectively.

Vaccination is one way to prevent infection; however, vaccines have not been developed for every viral disease. Western medicines based on herbal extracts, and alternative Eastern medicines have been used for treatment and as preventative measures in instances of viral infection. In particular, the latter has been developed based on daily life from ancient times when molecular biological knowledge was lacking. An example of this is the bark of *Cinchona succirubra*, which contains quinine and has been used as a remedy for malaria.

Following infection, certain viruses cause cytopathic effects (CPE) in cells that grow as monolayers *in vitro*. This phenomenon is a useful tool in virology to determine whether a material is applicable for treatment of viral diseases. Viral infection is usually controlled by species specificity, and inhibited by interferons produced by infected cells. Not every cell line exhibits a CPE following infection. African Green Monkey (Vero) cells (Yasumura & Kawakita, 1963) are defective in the production of interferons, and are highly susceptible to arboviruses and many other pathogenic viruses (Simizu & Terasima,). The Vero cell line is used for basic virus research in laboratories, diagnostics in hospitals, epidemiological surveys and bacterial toxin assays. Additionally, the potential of Vero cells for vaccine production has been examined. The cell line has been distributed to scientists globally by services such as the American Type Culture Collection.

It has been shown that *Agaricus blazei* Murille water extracts, prepared as an alternative medicine, inhibit the formation of CPE in Vero cell cultures caused by the WEE virus. Vero cells were continuously cultured in a modified Eagle's minimal essential medium without serum, protein and lipids (Yasumura et al., 1978). The cells were grown on 24-well plastic culture plates in a chemically defined medium for viral assay experiments, cells infected after they reached confluency. Before virus infection, the cells were washed with the phosphate-buffered saline (PBS, pH 7.4) without Mg^{2+} and Ca^{2+}. A virus-containing solution (0.2 ml) with a 50% tissue culture infective dose ($TCID_{50}$) of 100 was added to each well and

allowed to adsorb for 90 min at room temperature. The virus solution was then removed from the wells, and fresh culture medium with and without *Agaricus* extracts added (Sorimachi et al., 2001).

2. Effect of alternative medicine on viruses

2.1 Effect of Agaricus blazei water extracts on virus-infected VERO cells

When Vero cells were infected with WEE virus, CPE was observed as shown in Figure 1-D and Table 1. The original water extract from *Agaricus blazei* mycelia (A-0) and other fractions (A-1, A-2 and A-3) showed a significant inhibitory effect on CPE formation by WEE virus after 1 week in culture, but this effect was no longer observable after 2 weeks in culture (Table 1) (Sorimachi et al., 2001). Fractions A-4 and A-5 showed a small inhibitory effect on the occurrence of CPE induced by HSV (Table 1). However, neither the original water extracts of *Agaricus blazei* fruiting bodies nor their fractions obtained by ethanol precipitation demonstrated significant inhibitory effects on CPE due to WEE virus or HSV.

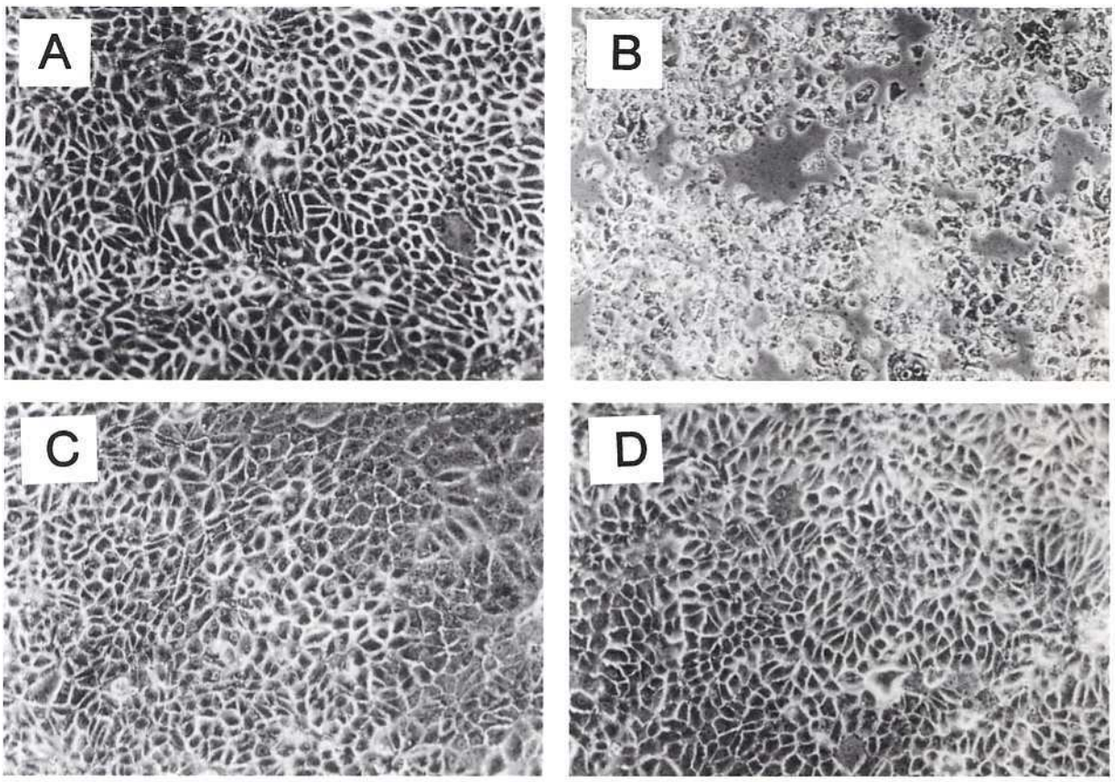

Fig. 1. Inhibitory effect of *Agaricus blazei* fractions on the CPE of Vero cells induced with western equine encephalitis (WEE) virus. Cells were infected with WEE virus and cultured for 1 week. (A) Control, uninfected Vero cells; (B) cells infected with WEE virus; (C) cells treated with fraction A-4; and (D) cells infected with WEE virus and cultured with fraction A-4. The concentration of *Agaricus* fraction A-4 was 100 μg/ml. This figure is reproduced from *Bioscience, Biotechnology and Biochemistry*, 65 (7); 1645–1647, 2001, and has been used with permission from Japan Society for Bioscience, Biotechnology, and Agrochemistry.

Fraction	Ethanol (%)	WEE	HSV
A-0	0	(++)	-
A-1	17	(+)	-
A-2	29	(++)	-
A-3	38	(++)	-
A-4	44	+++	(++)
A-5	50	+++	(+)
A-6	50 Sup	-	-

Table 1. Inhibitory effect of *Agaricus blazei* mycelia fractions on CPE induced by western equine encephalitis (WEE) virus and herpes simplex virus (HSV).
Cells were cultured for 2 weeks following virus inoculation.
(+), small inhibitory effect observed after 1 week in culture, but absent after 2 weeks in culture. (++), significant inhibitory effect observed after 1 week in culture, but no longer observable after 2 weeks in culture. +++, complete inhibition was observed after 2 weeks in culture. -, no significant inhibition was observed. The 50% tissue culture infective dose was 100. The concentration of *Agaricus* fractions was 100 μg/ml.

2.2 Effect of lignin derivatives on virus-infected VERO cells

Lignin derivatives, such as EP3, extracted from the culture medium of the edible Japanese mushroom, *Lentinus edodes*, inhibit the formation of CPE usually caused by HSV and WEE virus (Table 2) (Sorimachi et al., 1990). Other lignin derivatives, such as lignosulfonate (LS), obtained from the waste liquor of acid sulfite pulping processes, demonstrate similar anti-viral activity as EP3. Both EP3 and LS partially inhibit the formation of CPE caused by other viruses including polio, mumps and measles viruses. It is well known that a small proportion of measles cases can cause subacute sclerosing panencephalitis many years after the initial infection.

Virus	EP3	LS
Vaccinia	(+)	(+)
Herpes simplex		
(Yasumura, type 1)	+++	+++
(UR-3, type 1)	+++	+++
(UW, type 2)	+++	+++
(MS, type 2)	+++	+++
WEE	+++	+++
Polio	+	++
Mumps	+	+
Measles (Sugiyama)	+	+

Table 2. Inhibitory effects of EP3 and LS on CPE induced by various viruses.
+++, complete inhibition; ++, a few cytopathogenic effects were observed; +, a small effect was observed; and (+), a small drug effect was observed after 4 days in culture.

2.3 Effect of alternative medicines on HIV

Encephalitis caused by HIV is another serious problem that needs to be considered. HIV has been well characterized at a molecular biological level and clinically, but with a complete

remedy yet to be established. Reasons for this include antigenic variation of HIV surface proteins and a lack of adequate medications. The compound agaritine, which is a carcinogen and is contained in *Agaricus bisuporus* and *Agaricus blazei* Murrile, inhibits HIV protease activity (Gao et al., 2007). Although agaritine is found within alternative medicines and is toxic to healthy people, it is useful in treating HIV-positive patients. Additionally, the method to specifically remove agaritine from *Agaricus blazei* water extracts has been recently established in our laboratory (Koge et al., 2011). Thus, we can now select *Agaricus* water extracts with or without agaritine products depending on their end purpose. EP3 (Suzuki et al., 1989a) and LS (Suzuki et al., 1989b) showed anti-viral activity against HIV *in vitro*, and the oral administration of LEM, which contains EP3, improved the hepatic functions of hepatitis B patients *in vivo* without serious side effects. Therefore, *Agaricus blazei* extracts and lignin derivatives, which are used as alternative medicines, may be promising antiviral compounds, even though we do not understand the inhibitory mechanisms of these drugs on certain viruses *in vitro* or *in vivo*.

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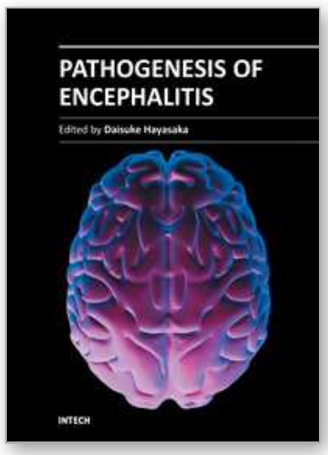

Pathogenesis of Encephalitis
Edited by Dr. Daisuke Hayasaka

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Many infectious agents, such as viruses, bacteria, and parasites, can cause inflammation of the central nervous system (CNS). Encephalitis is an inflammation of the brain parenchyma, which may result in a more advanced and serious disease meningoencephalitis. To establish accurate diagnosis and develop effective vaccines and drugs to overcome this disease, it is important to understand and elucidate the mechanism of its pathogenesis. This book, which is divided into four sections, provides comprehensive commentaries on encephalitis. The first section (6 chapters) covers diagnosis and clinical symptoms of encephalitis with some neurological disorders. The second section (5 chapters) reviews some virus infections with the outlines of inflammatory and chemokine responses. The third section (7 chapters) deals with the non-viral causative agents of encephalitis. The last section (4 chapters) discusses the experimental model of encephalitis. The different chapters of this book provide valuable and important information not only to the researchers, but also to the physician and health care workers.

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