

## **COVID-19 AND BRAIN DAMAGE: NON-TOXIC IRON CHELATORS CAN PREVENT ADEM AND BRAIN DAMAGE BY COVID-19**

**Yuzo Nishida**

Disease Absorption System Technologies Co., Ltd (DASTec). 920-0226 Kanazawa-city, Ishikawa-Pref. Japan. E-mail: nsd-2210@kanazawa-med.ac.jp

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**ABSTRACT:** *Based on the chemical mechanism of degradation of cholesterol and myelin, we would like to propose that non-toxic iron chelators including SP10, natural or artificial lignin derivatives can be the best supplement against COVID-19, especially to prevent brain damage including ADEM.*

**Keywords:** COVID-19, Brain damage, ADEM, Iron chelator

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### **INTRODUCTION**

Very recently British researchers have warned that the coronavirus pandemic could lead to a wave of brain damage in infected patients (Paterson et al. 2020). The experts at the University College London (UCL) were the latest to describe that COVID-19 could cause neurological complications including stroke, nerve damage, and potentially fatal brain inflammation; even if the patients didn't know show severe respiratory symptoms associated with the disease. Dr. M. Zandi has said that we should be vigilant and look out for these complications in people who have had COVID-19, and is warning that it remains to be seen "whether we will see an epidemic on a large scale of brain damage linked to the pandemic".

The study, published in the journal *Brain*, examined 43 patients treated at University College London Hospitals for either confirmed or suspected coronavirus, from April to May. They varied in age from 16 to 85, and showed a range of mild to severe symptoms. Among these patients, researchers found 10 cases of "temporary brain dysfunction" and delirium; 12 cases of brain inflammation; eight cases of strokes; and eight cases of nerve damage. Most of the patients who showed brain inflammation were diagnosed with a specific and sometimes deadly condition known as Acute disseminated encephalomyelitis (ADEM) (Paterson et al. 2020; Parsons et al. 2020). It should be noted here that in ADEM, the myelin sheath is destroyed, and this property is very similar to that observed for the patient with Multiple Sclerosis (Abe and Nishida, 2018), and the chemical

mechanism of the degradation of myelin sheath will be described in this paper.

## **NTBI AND NEURODEGENERATIVE DISORDERS**

Iron is an essential element for all living organisms and plays an important role in critical cellular processes such as energy production, cell proliferation, and DNA synthesis. Although adequate iron levels are essential for human health, iron overload causes some disorders such as hemochromatosis, which is often referred as iron overload diseases (Nishida, 2012, 2015a,b). In plasma of the patients with iron- overloading disorders, it is well known that the iron ion not associated with transferrin generally termed as non-transferrin-bound iron (NTBI), or labile plasma iron, is detected, and is present at concentration up to 10  $\mu$ M (Evans et al, 2008; Hershko et al, 2005). The iron-overload causes carcinogenesis in some organs, and the oxidative stress due to the abnormally high levels of NTBI demonstrated in a number of neurodegenerative disorders including dementia, and Alzheimer's disease, and Multiple sclerosis (MS) is believed to be associated with neuronal death in these disorders (Nishida, 2004; Gaeta & Hider, 2005; Stankiewicz et al. 2007).

In our previous paper (Abe, Sakiyama, Nishida, 2015), we have elucidated the role of the NTBI to induce the degradation of cholesterol, which is the main component of myelin sheath. According to the results, it seems clear that the degradation of myelin sheath may proceed through the degradation of cholesterol, which is performed by the iron (III) or copper (II) compounds with the dimeric structure, suggesting that the ADEM and MS can be induced by NTBI (Abe and Nishida, 2018). The NTBI in the COVID-19 patients may be accumulated from that for the proliferation of virus, much amount of iron ions are transported by transferrin, and the iron (III) ions used for proliferation are remained in the blood as NTBI, which may be transported to brain. The thrombosis, thrombotic stroke, inflammation, and nerve damage observed in COVID-19 patients should be related with this NTBI through the formation of a dangerous  $\mu$ -oxo bridged dimeric iron (III) species (Nishida 2012, 2015a,b).

Thus, depletion of NTBI by an iron chelator has been explored as a possible therapeutic intervention in cancer (Nishida, 2012, 2015a, 2015b) and also COVID-19. In facts, some iron chelators have been shown to inhibit cancer cell proliferation, either alone or in combination with other anti-cancer drugs (Ohara et al, 2013; 2018). However, iron

chelators can cause potentially serious side effects (Ohara et al., 2018). For example, deferasirox or *Exjade* in Figure 1, an oral iron chelator, has superior iron chelation ability, but cause digestive, liver, and kidney disorders. Deferoxamine (DFO) is an intravenous iron chelator that also exhibits toxic side effects. Decreasing the side effects of iron chelators may improve cancer treatment compliance, thereby improving clinical outcomes.

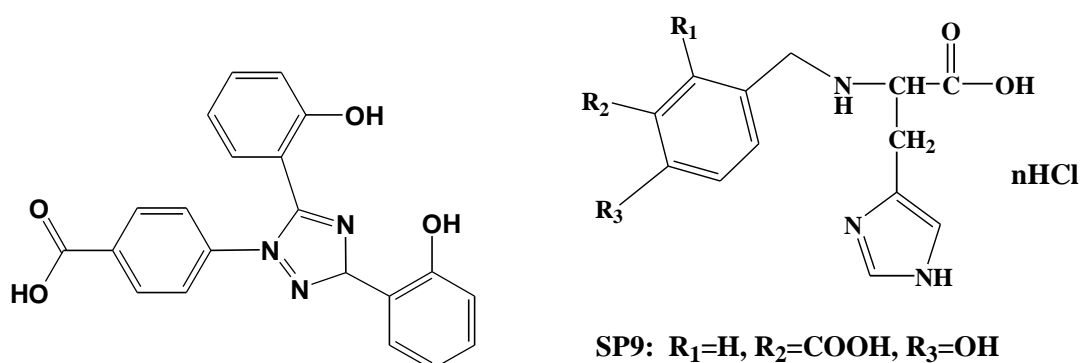


Figure 1. left; Exjade right; Nishida's chelates;  $n=1$  for SP9,  $n=2$  for SP10

### NEW NON-TOXIC IRON CHELATOR, SP10

Nishida has succeeded in synthesis of novel iron chelators named as Super-polyphenols (Nishida, 2012; 2015), which are shown to be non-toxic with reduced side effects, two examples of water-soluble super-polyphenols, SP9 and SP10, being illustrated in Figure 1 (Nishida, 2019). The non-toxicity of these compounds exemplified by Ohara et al. (Ohara et al, 2018) should be due to that these compounds cannot be a substrate for cytochrome P450 because of its hydrophilicity, and also to that the iron (III)-chelates of these super polyphenols are non-toxic, which is strongly supported by the studies on the chemical mechanism of the toxicity induced by the iron (III) with artificial chelates in human body done by Nishida (Nishida, 2012). The most important point is that these two chelates do not form a dangerous  $\mu$ -oxo bridged dimeric iron (III) species, which has been pointed out to be main species to induce iron toxicity by NTBI (Nishida, 2012, 2019).

Ohara et al. have reported that SP10 inhibited cancer cell proliferation by inducing apoptosis in HCT116, HSC-2, A549, and MCF-7 cancer cells *in vitro*, and that SP10 and

SP9 are shown to inhibit tumor growth in an HCT116 and A549 xenograft models *in vivo*, respectively (Ohara et al. 2018, Nishida 2020a). The anti-tumor ability observed for SP10 may be attributed to that SP10 binds with Fe(III) ion in NTBI, changing the chemical nature of the iron(III) ion; especially preventing the transfer of iron(III) ion from NTBI to apo-transferrin; in these cases cancer cell proliferation is retarded because of the deficiency of the iron ions (Nishida, 2019; 2020a,b). In addition to above facts, Ohara et al. also observed that SP10 can depress the infection by human influenza virus PR8 (Nishida, 2020a,b), supporting that SP10 controls the chemical properties of NTBI, inhibiting the growth of influenza virus.

### **NON-TOXIC IRON CHELATORS TO PREVENT ADEM and BRAIN DAMAGE BY COVID-19**

The water-soluble lignin in the extract of the solid culture medium of *Lentinus edodes* mycelia has been known to have antiviral and immunopotentiating activities *in vivo* and *in vitro* (Yamamoto et al. 1996). It should be noted that both the water-soluble and water-insoluble lignin derivatives contain phenolic group such as catechol and vanillin, *etc.*, and these phenolic compounds can form the iron(III) compounds with iron(III) ions of NTBI, preventing the growth of virus, similarly as observed for the SP10 (Nishida, 2020a). Based on the above discussion it seems quite likely that lignin derivatives can retard the formation of a dangerous  $\mu$ -oxo bridged dimeric iron (III) species, which should lead to the prevention of degradation of myelin sheath in ADEM and multiple sclerosis patients.

It is well known that Japanese food contains many types of roots, leaves, and stems of the plants, where many types of lignins derivatives (both water-soluble and water-insoluble) are included. Thus, Japanese food and also SP10 seem to be very useful to prevent ADEM and brain damage in the patients of COVID-19 as mentioned above, and this may elucidate the origin of “Japanese Paradox”, the extremely reduced deaths from the COVID-19 in Japan (Nishida 2020b,c).

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