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ON THE CHEMICAL PROPERTIES OF TRADITIONAL CHINESE MEDICINES

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

ABSTRACTS: *The Chinese government is heavily promoting traditional Chinese medicines (TCM) as treatment for COVID-19 at present, but there are no rigorous trial data to demonstrate that the remedies work. Based on our recent works, we have elucidated the chemical properties of TCM, and have proposed the scientific origin of "Japan Paradox".*

KEYWORDS: Chinese medicines, iron chelator, anti-viral activity, COVID-19

INTRODUCTION

The current outbreak of the novel coronavirus COVID-19, epi-centered in Hubei Province of the People's Republic of China, has spread to many countries. Since there is no specific drug and vaccine for COVID-19, the treatment is mainly symptomatic supportive therapy (Cyranoski, 2020). The Chinese government is heavily promoting traditional Chinese medicines (TCM) as treatments for COVID-19 at present. The remedies, a major part of China's health-care system, are even being sent to countries including Iran and Italy as international aids. But, scientists outside China say it is dangerous to support therapies that have yet to be proved safe and effective. In China, senior officials and state media are pushing a range of TCM as being effective at alleviating COVID-19 symptoms and reducing deaths from the diseases. However, there are no rigorous trial data to demonstrate that that remedies work (Cyranoski, 2020). Our recent works can clearly give answer for the above questions.

TOXICITY DUE TO NON-TRANSFERRIN-BOUND IRON (NTBI)

It is well known that ion 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, 2015). 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 μM (Evans et al. 2008; Hershko et al. 2005). The iron-overload causes carcinogenesis in some organs and a number of neurodegenerative disorders including dementia, and Alzheimer's disease (Nishida, 2004; Gaeta & Hider, 2005).

NON-TOXIC IRON CHELATOR, SP10, CATECHOL DERIVATIVE

Thus, depletion of NTBI by an iron chelator has been explored as a possible therapeutic intervention in cancer and neurodegeneration (Nishida, 2012) 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*, 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.

Nishida has in the first time succeeded in synthesis of novel iron chelators named as Super-polyphenols (Nishida, 2019; 2020), 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; 2020). 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, 2019; 2020).

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). 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 cell proliferation is stopped because of the deficiency of the iron ions (Nishida, .2019; 2020) In addition to above facts, Ohara et al. also observed that SP10 can depress the infection by human influenza virus PR8 (Nishida, 2020), supporting that SP10 controls the chemical properties of NTBI, inhibiting the growth of influenza virus.

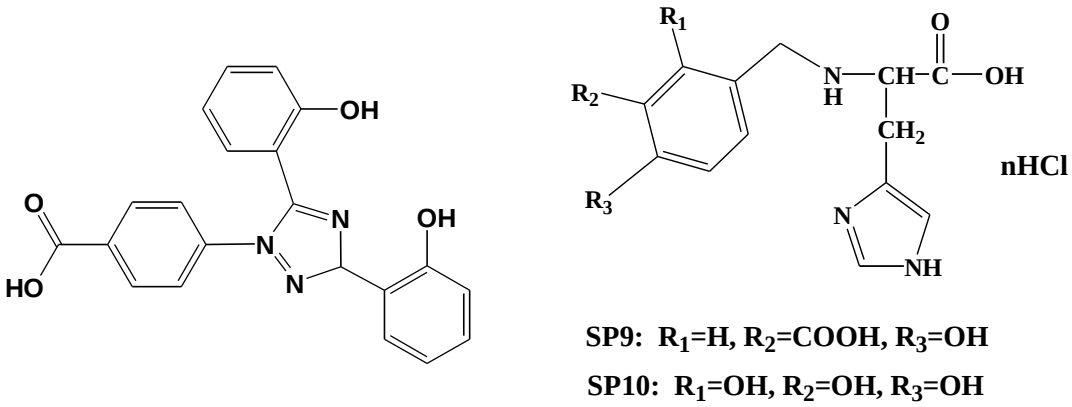

Figure 1. left; Exjade right; Nishida's chelates; n=1 for SP9, n=2 for SP10

RELATIONSHIP BETWEEN LIGNIN DERIVATIVE AND CHINESE MEDICINE

It seems to be very interesting to point out that 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); chemical structures of the water-soluble lignin are illustrated in Figure 2. It should be noted that in the water-soluble lignin (in Figure 2, lower side), there are many compounds having phenolic group such as catechol and vanillin, etc., and thus the antiviral and immunopotentiating activities of the water-soluble lignins (Yamamoto et al. 1996) may be rationalized on the assumption that these phenolic compounds control the chemical properties of the iron (III) ions of NTBI, preventing the growth of virus, similarly as observed for the SP10 (Nishida, 2020).

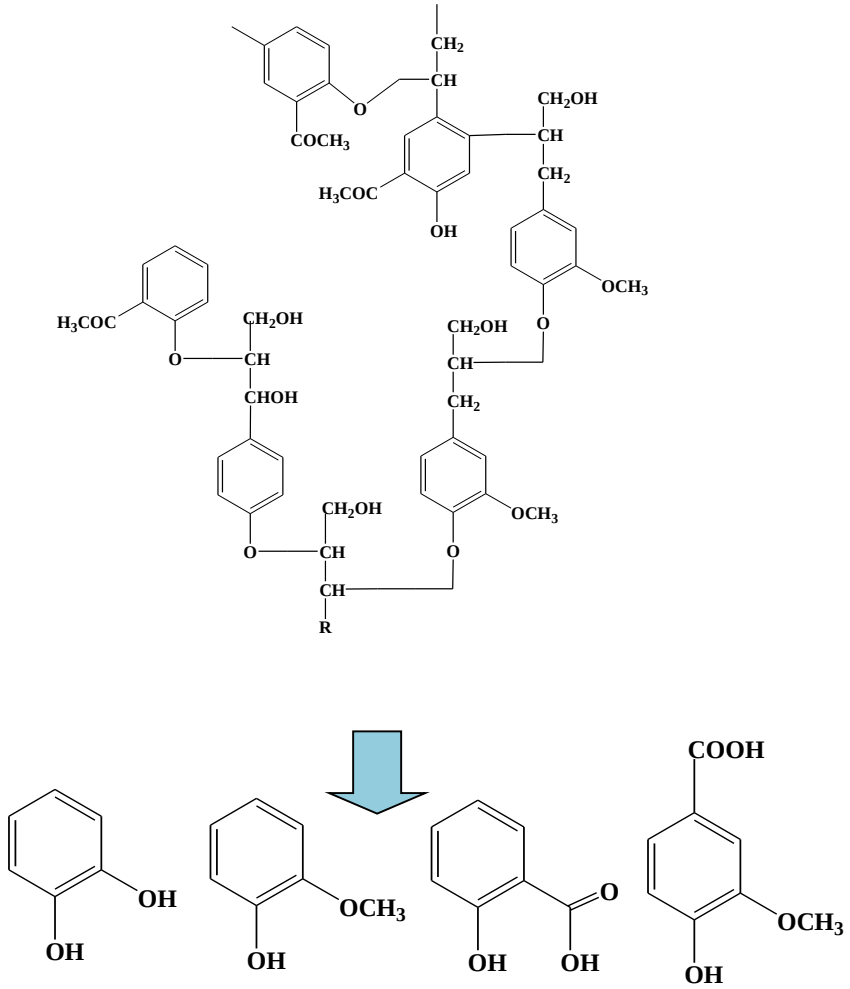

Figure 2: Upper: Chemical structure of lignin. Lower: examples of the compounds contained in the water-soluble lignin derived through enzymatic reaction (Yamamoto et al. 1996; Kasai et al., 2007).

The traditional Chinese medicines are mainly produced from various roots, leaves including herbs, and stems of the plants (Cyranoski, 2020). It should be noted that many types of lignins are included in these roots, leaves, and stems, and thus TCM should contain many types of phenolic compounds, which are the chelators for iron(III) ions, and thus it is anticipated that TCM may exhibit both the antiviral and immunopotentiating activities in vivo and in vitro, similarly to the cases of water-soluble lignins (Yamamoto et al. 1996) and SP10 (Nishida 2020). In addition to these, it should be remembered that

Exjade, one of the phenolic iron(III) chelator in Figure 1, exhibits severe side-effects, completely different from those SP9 and SP10, almost non-toxic compounds. As the TCM may contain phenolic compounds of both dangerous and non-toxic compounds as Exjade and SP10, respectively, and thus it seems to be reasonable to consider that TCM are sometimes non-toxic and work effectively to depress the infection of COVID-19, but at some times it exhibits high side-effects.

SCIENTIFIC ORIGIN OF "JAPAN PARADOX"

In the ordinary days, Japanese peoples usually take so-called Japanese-food (washoku), which contains many types of vegetables including lignin derivatives, and also drink Japanese tea, which contains many types of catechins, catechol derivatives. This may explain the origin of "Japan Paradox", the extremely reduced deaths from the COVID-19 in Japan.

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