New Non-toxic Iron Chelators SP9 and SP10 and Its Potentiality as Brain Supplement

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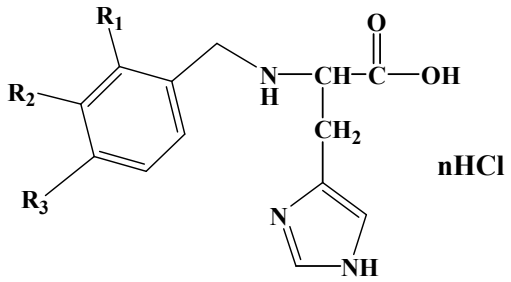
Iron is an essential element for all living organisms and plays an important role in critical cellular processes such as energy production and DNA synthesis. [1] Although adequate iron levels are essential for human health, iron overload causes some disorders such as hemochromatosis, and carcinogenesis in some organs. 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, and the oxidative stress due to the abnormally high levels of NTBI demonstrated in a number of neurodegenerative disorders including *dementia*, Parkinson's disease (PD) and Alzheimer's disease (AD), is believed to be associated with neuronal death in these disorders. [1]

Thus, depletion of NTBI by an iron chelator has been explored as a possible therapeutic intervention in both cancer and neurodegeneration. In facts, some iron chelators have been shown to inhibit cancer cell proliferation, either alone or in combination with other anti-cancer drugs. [2] However, iron chelators can cause potentially serious side effects. For example, deferasirox (DFX, 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, [2] and this should be also applied to therapy for neurodegeneration.

Nishida has succeeded in synthesizing the novel iron chelators, which are shown to be non-toxic with reduced side effects, named as Super-polyphenols, [1,3,4] and two examples of water-soluble super-polyphenol, SP9 and SP10, are illustrated in Figure 1. The non-toxicity of these compounds exemplified by Ohara et al. [2,3] should be due to that these compounds cannot be a substrate for cytochrome P450 because of its hydrophilicity [5], 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

[1,5,6]; the most important point is that these two chelators do not form a dangerous μ-oxo bridged dimeric iron (III) species (see Figure 2).



SP9: R_1=H, R_2=COOH, R_3=OH

SP10: R_1=OH, R_2=OH, R_3=OH

Figure 1. Chemical structures of SP9 (n=1) and SP10 (n=2).

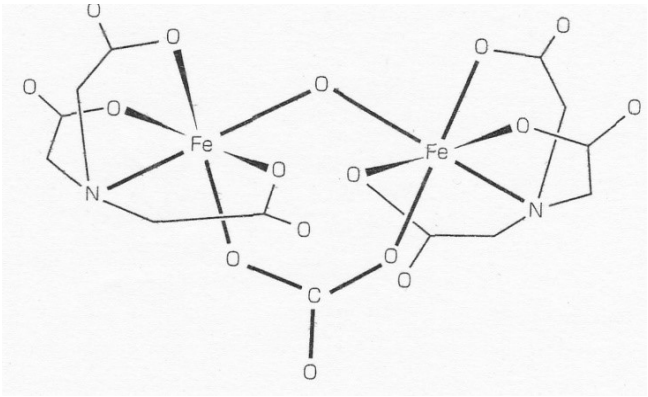


Figure 2. The structure of μ-oxo bridged dimeric iron (III) species with (nta) (nta represents nitrilotriacetic acid), $[Fe_2O(nta)_2(CO_3)]^{4-}$ [1,5-7]. The oxygen atom bridged by two iron (III) atoms is di-negative *oxo*-anion The strong trans-effect by the short Fe-*oxo* bond rejects the co-existence of two bonds with Fe-O (phenolic molecule) and Fe-O (*oxo* atom) in the same molecule, preventing the formation of μ-oxo bridged dimeric iron (III) species with SP9 or SP10 [6,7].

Ohara et al. [2,3] 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 depresses the infection by human influenza virus PR8.

In addition to these, *oral* administration of SP10 and SP9 are shown to inhibit tumor growth *in vivo* in an HCT116 and A549 xenograft models (nude mouse), respectively. [2,3] According to Tomono *et al*., the anti-tumor effect of Exjade (Deferasirox) on A549 xenograft model was almost the same as that of SP9 under the same experimental conditions. Drs. Okuda and Sugimoto at Doshisha University have administrated *orally* SP9 and SP10 in the drinking water (0.5 %) for 9 weeks to the APP/PS1 transgenic mouse with brain where excess amyloid β-proteins are present to form senile plaques, and found that none of 18 mice died after administration of SP9 and SP10, although two of 9 mice died in the control system without SP9 or SP10, implying that the presence of SP9 or SP10 depresses the toxicity due to the amyloid β-proteins.

All the above facts are suggesting that new non-toxic iron chelator SP10 can be a good *oral* brain supplement, and we can supply SP10 to all the researchers who want to use SP10 for their studies.

References

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