

## Science "Special" Seminar

## Can Resveratrol be the Multidrug in Longevity Society?

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Polyphenol is general term for botanical constituent has phenolic hydroxyl in molecule, including catechin, chlorogenic acid, or flavonoids such as daizein and quercetin. The polyphenol in foods is not essential nutrients, which used as energy or body structural component, but it has many physiological functions and started to use in supplement. Especially, the most attractive polyphenol is resveratrol, found from red wine, recently.

### Physiological active substance in red wine polyphenol

Resveratrol (3,4',5-trihydroxy-*trans*-stilbene) is botanical antibacterial agent called phytoalexin, produced for protecting from fungus or bacteria, and structured three hydroxyl on stilbene skeleton (Fig.1). Resveratrol is rich in grape and peanuts skin. Also, it is well known polyphenol rich in red wine may explain French paradox, the French consume high fat diet much more than other Europeans but relatively low mortality by ischemic cardiac disease. Initially, resveratrol has emphasized by preventing arteriosclerosis, pathogenesis of ischemic cardiac disease, from its powerful antioxidant effect via inhibit blood low density lipoprotein (LDL) oxidation and reduce the form cell formation macrophage uptake LDL and suppress deposition to vascular wall.<sup>1)</sup> Also, resveratrol is well known for estrogenic activity, antiinflammation, and antitumor action.

On the other hand, longevity phenomenon is well known while yeast was energy restriction, silent information regulator 2 (sir2) is activated and increasing division frequency.<sup>2)</sup> Resveratrol is the one has the effect that activating sir2 without energy restriction to yeast,<sup>3)</sup> as well as *C. elegans* and *drosophila*, therefore, resveratrol has been attracted for

longevity. Eventually, in 2006, resveratrol had reported extend life span on high fat diet.<sup>4)</sup> At this stage, extending life span effect is different in mammalian from the yeast. It improves various symptoms of lifestyle-related disease under the condition of high fat diet, improve impaired glucose tolerance by obesity, improve exercise function and its rising energy expenditure by mitochondrial hyperactivity, moreover, ward off dementia by improving brain function. In this longevity society, resveratrol expected as preventing/treating various diseases.

The mechanism for extending lifespan of resveratrol is thought to be mediated by SIRT1, human homolog of sir2, researching for resveratrol-related substance and drug development targeting for SIRT1 activation. There are amount of modified resveratrol complex have synthesized and some of them are over thousands times effective than resveratrol.<sup>5)</sup> In 2012, clinical research of SIRT1 activator was reported, and pharmaceutical products from resveratrol would be developed in the near future.

### The structure of resveratrol and its bioactivities

Resveratrol has two geometrical isomers that are *trans* and *cis* forms in binding between A and B rings in the nature. *Trans*-resveratrol has strong bioactivity and the 4-hydroxy group is essential for antioxidation like radical scavenging ability. Conversely, strong radical scavenging ability might impinge for biological reaction. Resveratrol has been reported as genotoxicity like sister chromatid exchanges (SCE), and even thousandth of mitomycin, SCE inducer, concentration, resveratrol inhibit cell proliferation on concentration dependency.<sup>6)</sup> Genotoxicity disappeared when 3-hydroxy group has removed. Interestingly, both of diethylstilbestrol (DES), endocrine disrupting chemical, and

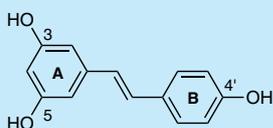


Fig.1 Structure of resveratrol

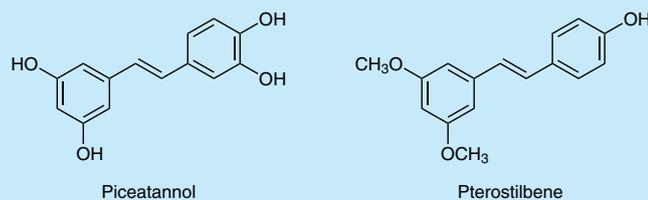


Fig.2 Structure of resveratrol analogues

4-hydroxy tamoxifen, activates metabolite of drug for cancer treatment called tamoxifen, have 4-hydroxy group as well as resveratrol. However, all of bioactivities of resveratrol could not be explained by antioxidation of 4-hydroxy group. Even 4-hydroxy group has removed, bioactivities are still remained in some cases. Therefore, the relationship of these structure and bioactivity will beneficial information for drug development from resveratrol analogues.

### Resveratrol analogues in the nature

Piceatannol (3,4,3',5'-tetrahydroxy-*trans*-stilbene), has four hydroxy group, or pterostilbene (3,5-dimethoxy-4'-hydroxy-*trans*-stilbene), 3-hydroxy and 5-hydroxy is substitute for methoxy, are resveratrol inductor with bioactivity in the nature (Fig. 2). Resveratrol can be found in grape, peanuts and berries like blueberry or bilberry. In the berries, *trans*-resveratrol, piceatannol, and pterostilbene are contained and those concentration could be changed depend on the race, growing condition or climate. Piceatannol has bioactivity like resveratrol but its mechanism is not the same. In consequence of substituting hydroxyl for methoxy in pterostilbene, it remains intracellularly and bioavailability is higher than resveratrol and expecting other physiological function other than resveratrol.

Due to the usage for the ingredient is limited to extract from natural plant for the supplement in the health food, those derivative concentration in the ingredient might determine the efficacy and price of the supplement. Root of Japanese knotweed, Kojokon, contains *trans*-resveratrol and its glycoside still more than grapes and does not contain *cis*-, therefore, it is used as the ingredient of resveratrol in overseas, recently. Unfortunately, in Japan, root of Japanese knotweed has been used as herbal medicine "polygonum cuspidatum root" and it cannot be used as a supplement under the pharmaceutical affairs law.

### The advantages of polyphenol...

Polyphenol such as resveratrol is not essential nutrient as mentioned at the beginning. Mechanism to digest and absorb the nutrient into the body for human and animals is quite different with those for polyphenol. Most of the polyphenol is metabolized by drug-metabolizing system, thus, even that is efficacy to the body, it is metabolized quickly. Several polyphenol that effective for the body is found from foods which regularly intake everyday, such as catechin in tea, coffee polyphenol, resveratrol in wine, and isoflavone in miso soup. Considerations for polyphenol intake as supplement are amount and timing, as well as safety.

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### Introduction of the author :

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Yoko Fujiwara received her Ph.D. from Ochanomizu University in 1993. Later, she worked as a research fellow of Japan Foundation for Aging and Health, Baker Medical Research Institute and then, Japan Health Sciences Foundation. In 1997, she joined Ochanomizu University as a lecturer. She was appointed to a Professor-ship in 2010.

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