Effect of Resveratrol Dimers and Tetramers Isolated from Vitaceous and Dipterocarpaceous Plants on Human SIRT1 Enzyme Activity

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Submission date: 17-May-2019 03:03PM (UTC+0800)
Submission ID: 1131915695
File name: NPC-13-11-1531-2018.pdf (986.17K)
Word count: 4853
Character count: 28830

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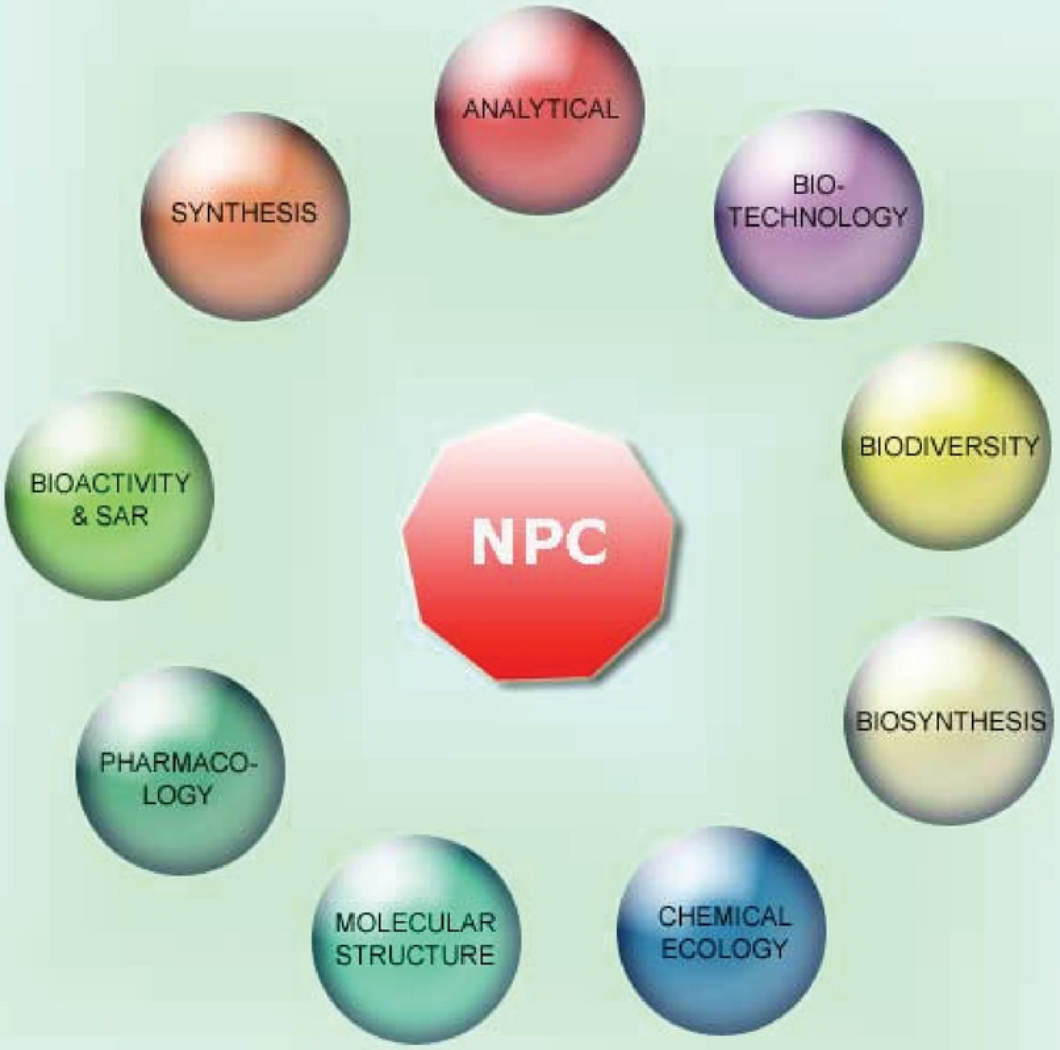

Volume 13. Issue 11. Pages 1419-1568. 2018
ISSN 1934-578X (printed); ISSN 1555-9475 (online)
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NPC Natural Product Communications

2018
Vol. 13
No. 11
1531 - 1534

Effect of Resveratrol Dimers and Tetramers Isolated from Vitaceous and Dipterocarpaceous Plants on Human SIRT1 Enzyme Activity

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Received: May 15th, 2018; Accepted: August 9th, 2018

SIRT1 is a mammalian ortholog of the yeast enzyme Sir2, which is an NAD^+-dependent deacetylase of histones, p53, FOXO, NF-κB, PGC-1α, and other transcription factors. The Sir2 protein is reported as a longevity protein in yeast. Resveratrol, a polyphenol isolated from various types of plant families, particularly the Vitaceae family, is a known naturally occurring SIRT1 activator. In this study, we evaluated the effects of four types of resveratrol dimers and four types of tetramers isolated from vitaceous plants, and one type of resveratrol tetramer isolated from a dipterocarpaceous plant on purified human SIRT1 enzyme activity. Of the resveratrol dimers examined, (+)-ε-viniferin and pallidol exhibited no effect on SIRT1 enzyme activity, whereas (+)-ampelopsin B and (−)-ampelopsin F showed inhibitory activity on SIRT1. However, all the resveratrol tetramers examined, i.e., (+)-vitisin A, (−)-vitisin B, (+)-hopeaphenol, (−)-hopeaphenol, and (−)-isohopeaphenol markedly inhibited the human SIRT1 enzyme activity. (+)-Hopeaphenol exhibited the most potent inhibitory activity, which was comparable with that exhibited by a known SIRT1 inhibitor suramin. Since SIRT1 inhibitors reportedly possess anticancer activity, (+)-hopeaphenol and other resveratrol oligomers can be used as a seed compound for anticancer drugs.

Keywords: Sirtuin, Resveratrol oligomer, (+)-Hopeaphenol, SIRT1 inhibitor.

Sirtuins are members of a family of yeast silent information regulator 2 (Sir2), which are NAD^+-dependent protein deacetylases that promote yeast longevity [1, 2]. DNA sequences of sirtuins are highly conserved from bacteria to humans [3]. Seven types of sirtuins (SIRT1–SIRT7) are found in mammals, and SIRT1 is a mammalian ortholog of yeast Sir2 [4, 5]. SIRT1 has been most extensively studied in the contexts of aging and longevity in mammals [6]. It catalyzes the deacetylation of many proteins, including histones and transcription factors such as p53, FOXO, NF-κB, and PGC-1α [6, 7], and activates stress defense and DNA repair mechanisms, thus aiding the preservation of genomic integrity [8]. SIRT1 also functions in the regulation of metabolism and has thus been described as a potential tumor suppressor gene [9]. Reportedly, SIRT1 has a pivotal role in the pathophysiology of various metabolic and neurodegenerative diseases as well as cancers [6, 8-11].

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene), a phytoalexin isolated from vitaceous plants such as *Vitis vinifera* [12], is a well-known small molecule activator of SIRT1 [13, 14]. Resveratrol and many resveratrol oligomers (oligostilbenes) have been isolated from plants of families, such as Vitaceae, Dipterocarpaceae, Leguminosae, Cyperaceae, and Gnetaceae, and their chemical structures have been elucidated [15]. Resveratrol and its oligomers have been reported to exhibit inhibitory activity against cancer cell proliferation [16-19] and anti-inflammatory activity against lipopolysaccharide-induced arthritis [20].

Because resveratrol is an effective activator of SIRT1, it will be interesting to examine whether the resveratrol oligomers have the ability to regulate the SIRT1 enzyme activity. In the present study, we evaluated the effects of resveratrol dimers and tetramers (Figure 1) isolated from vitaceous plants and a tetramer isolated from dipterocarpaceous plants on recombinant human SIRT1 (rhSIRT1) enzyme activity.

His-tagged rhSIRT1 was expressed using the *Escherichia coli* (*E. coli*) expression system and purified by Ni^{2+}-Sepharose affinity chromatography. The enzyme showed a single band on SDS-polyacrylamide gel electrophoresis (SDS-PAGE) (Figure 2a). The molecular weight estimated using SDS-PAGE was larger than the value estimated from the cDNA sequence of hSIRT1 (84 kDa). Although the reason for this discrepancy remains unknown, the protein band was identified as SIRT1 by western blotting (Figure 2a).

Table 1: Effect of resveratrol and related compounds on rhSIRT1 enzyme activity.

Compounds		Relative enzyme activity
resveratrol	monomer	7.51 ± 0.76**
(+)-ε-viniferin	dimer	1.47 ± 0.27
pallidol	dimer	0.876 ± 0.059
(+)-ampelopsin B	dimer	0.741 ± 0.051*
(−)-ampelopsin F	dimer	0.014 ± 0.005**
(+)-vitisin A	tetramer	0.147 ± 0.140**
(−)-vitisin B	tetramer	0.033 ± 0.003**
(+)-hopeaphenol	tetramer	0.018 ± 0.018**
(−)-hopeaphenol	tetramer	0.002 ± 0.002**
(−)-isohopeaphenol	tetramer	0.045 ± 0.024**

The concentration of each compound is 100 μM. Enzyme activity is expressed relative to the control (DMSO), which was taken as 1.0. Data are expressed as the average ± SE from three independent experiments. *P<0.05, **P<0.01 by one-sample t-test

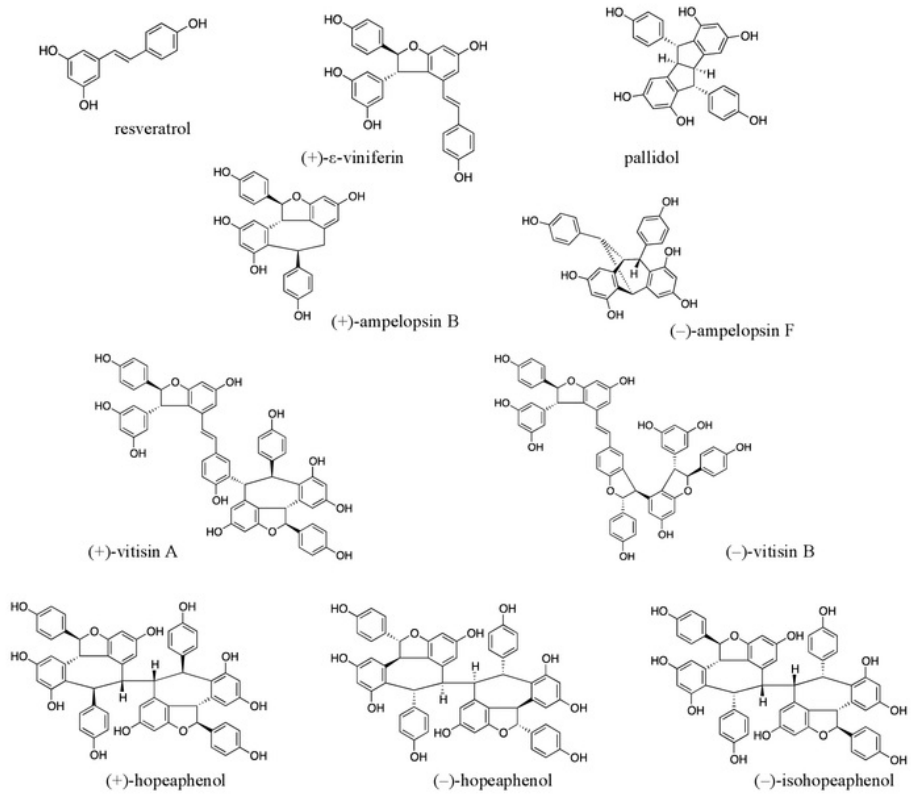


Figure 1: Structures of resveratrol oligomers isolated from vitaceous or dipterocarpaceous plants.

The structural and functional integrity of the purified rhSIRT1 was demonstrated by measuring the enzyme activity using a fluorescent derivative of p53 tetrapeptide. Fluorescence intensity was linearly increased, as a function of the concentration of the enzyme present (Figure 2b). The effect of resveratrol on the purified rhSIRT1 enzyme was then examined. As shown in Table 1, resveratrol enhanced the enzyme activity 7.5-fold higher than that in the control. These results indicated that rhSIRT1 used in the study had an intact and native conformation with sufficient enzyme activity, which is essential for regulating protein function by small molecules.

The effect of resveratrol oligomers at a concentration of 100 μM on the enzyme activity is shown in Table 1. Among the resveratrol dimers examined, (+)-ε-viniferin and pallidol exhibited no effect on the rhSIRT1 enzyme activity, whereas (+)-ampelopsin B and (−)-ampelopsin F exhibited an inhibitory effect. However, all of the resveratrol tetramers examined, i.e., (+)-vitisin A, (−)-vitisin B, (+)-hopeaphenol, (−)-hopeaphenol, and (−)-isohopeaphenol markedly inhibited rhSIRT1 enzyme activity.

Next, we evaluated the dose dependency of the compounds possessing inhibitory activity on rhSIRT1 and determined their IC_{50} values (Figure 3). (+)-Ampelopsin B was excluded as its IC_{50} value was estimated to be higher than 100 μM. Of the compounds examined, (+)-hopeaphenol showed the most potent inhibition of rhSIRT1, with an IC_{50} value of 3.45 μM, which was almost comparable with that of suramin (1.71 μM), a known inhibitor of SIRT1. The other compounds exhibited moderate inhibitory activity (IC_{50} =18.1–24.4 μM).

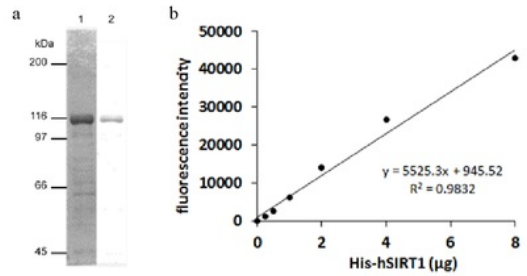
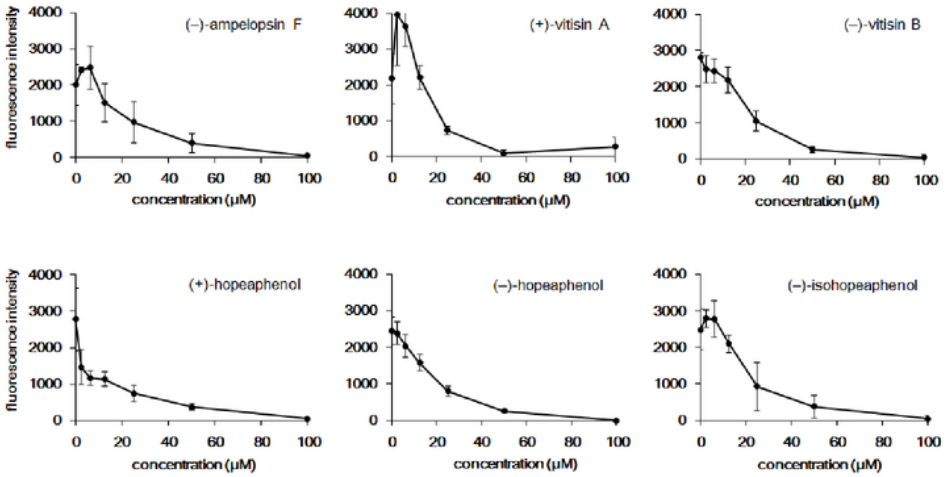


Figure 2: Characterization of the purified His-tagged rhSIRT1. a, SDS-PAGE and western blotting. His-tagged rhSIRT1 was expressed using the *E. coli* expression system and purified by affinity column chromatography. The purified His-tagged rhSIRT1 was analyzed by SDS-PAGE (lane 1, 5 μg) and western blotting (lane 2, 2 μg) as described in Experimental. b, Enzyme activity of the purified His-tagged rhSIRT1. Fluorescence intensity is in an arbitrary unit.

Resveratrol is known to be a direct activator of SIRT1 [13,14]. Reportedly, two resveratrol molecules can interact with the N-terminal domain of SIRT1, which is responsible for promoting tighter binding between SIRT1 and its peptide substrate, thus stimulating SIRT1 activity [21]. In a preliminary enzyme kinetics analysis, we observed that (+)-hopeaphenol interacts competitively with SIRT1 protein at the NAD^+ binding site. Distinct binding sites may explain the differences in the effects (activation or inhibition) of these small molecules. For better understanding of this aspect, a molecular docking study is underway to elucidate the accurate binding conformation of (+)-hopeaphenol with SIRT1.



compounds	(–)- ampelopsin F	(+)-vitisin A	(–)-vitisin B	(+)-hopeaphenol	(–)-hopeaphenol	(–)-isohopeaphenol	suramin
IC_{50} (μM)	24.4	22.0	21.1	3.45	18.1	21.6	1.71

Figure 3: Inhibitory effect of the six types of resveratrol oligomers on the hSIRT1 enzyme activity and their IC_{50} values. Dose dependency of the compounds on the hSIRT1 enzyme activity was measured at concentrations of 0–100 μM and expressed as the average ± SE from three independent experiments. IC_{50} value was defined as the concentration of a compound required to reduce the hSIRT1 enzyme activity by 50% compared with that of vehicle (DMSO). Suramin, a known inhibitor of SIRT1, was used as a standard.

Small molecule SIRT1 inhibitors have been reported to repress the growth of cancer cells and show potential as anticancer drugs [9, 16-19]. Because (+)-hopeaphenol and other resveratrol oligomers possess inhibitory activity on SIRT1, they can be used as a seed compound for anticancer drugs.

Experimental

Materials: Restriction enzymes were purchased from Toyobo (Otsu, Japan), and the bacterial expression vector pET-14b was from Novagen (Darmstadt, Germany). Resveratrol and related oligostilbenes (Figure 1) were isolated from vitaceous and dipterocarpaceous plants as previously described [22-27]. The structures of all test compounds were confirmed by spectroscopic measurements. All the test compounds were dissolved in a 50-mM dimethyl sulfoxide (DMSO) stock solution and stored at −80°C. All other chemicals used were of reagent grade.

Expression and purification of rhSIRT1: hSIRT1 cDNA was obtained by PCR from a human lung cDNA library (BioChain, Hayward, CA, USA). Nucleotide sequences of the primers used for PCR were as follows: Forward primer: 5′-ACAGGATCCATGGCGGACGAGGCGGCCCTCGC-3′; Reverse primer: 5′-CAGGTCGACGTGGAACAATTCCTGTACCTGCAC-3′. A full-length hSIRT1 cDNA was subcloned into pET-14b vector at the *Bam*H I and *Xho* I sites to construct the plasmid pET-hSIRT1, which expressed a recombinant 6× His-tagged fusion protein for hSIRT1. The pET-hSIRT1 plasmid was introduced into *E. coli* strain BL21 (DE3). The expression and purification of rhSIRT1 from the bacteria were performed according to the method previously described [28], with some modifications. The *E. coli* cells were incubated overnight at 37° C in Luria–Bertani (LB) broth (Lennox; Difco, BD, Franklin Lakes, NJ, USA) containing 100 μg/mL ampicillin. The overnight incubated culture was then inoculated into 250 mL of fresh LB broth (ratio, 1: 100) containing 100 μg/mL ampicillin and incubated at 30°C for 4 h with vigorous shaking until the OD_{600} reached 0.7–1.0. Expression of the recombinant protein was induced by overnight incubation (OD_{600}: 1.2–1.7) at 18°C in the presence of 1 mM isopropyl-*β*-D-thiogalactopyranoside. After incubation and subsequent centrifugation, the bacterial pellet was homogenized in 2.5 mL of 30 mM Tris-HCl buffer, pH 7.5, containing 1 mM EDTA and 1 mM dithiothreitol (DTT), on ice using an ultrasonic homogenizer. The homogenate was centrifuged at 543,200 ×*g* for 15 min at 4°C, and the supernatant was first applied to a PD-10 column (GE Healthcare, Uppsala, Sweden) to replace the buffer into a binding buffer comprising 20 mM sodium phosphate, 500 mM NaCl, and 40 mM imidazole (pH 7.4), and then applied to a Ni^{2+}-chelating affinity column (HisTrap™ HP, 1 mL; GE Healthcare) pre-equilibrated with the binding buffer. After washing the column with binding buffer, the enzyme was eluted with an elution buffer comprising 20 mM sodium phosphate, 500 mM NaCl, and 500 mM imidazole (pH 7.4). The yield of the purified enzyme was approximately 10 mg from 1 L of bacterial culture. The purified enzyme was stored in a solution of 25 mM Tris-HCl buffer (pH 7.5), 10% glycerol, 100 mM NaCl, and 5 mM DTT at −80°C.

SDS-PAGE and western blotting: SDS-PAGE was performed according to the method described by Laemmli [29] using a 7.5% polyacrylamide gel, and was followed by western blotting. After electrophoresis, the proteins were transferred onto polyvinylidene difluoride membranes (Millipore, Bedford, MA, USA) and incubated with anti-6× His-tag goat IgG (1:1,000 dilution in blocking buffer of 2% bovine serum albumin, Thermo Scientific, Rockford, IL, USA). After washing and incubating with alkaline phosphatase-conjugated anti-goat IgG (1:2,000 dilution in blocking buffer, Sigma, St. Louis, MO, USA), immunoreactive bands were visualized using nitroblue tetrazolium/5-bromo-4-chloro-3-indolyl phosphate (NBT/BCIP, Roche, Mannheim, Germany).

rhSIRT1 enzyme assay: His-tagged rhSIRT1 enzyme activity was measured using the *Fluor de Lys* SIRT1 fluorometric drug discovery assay kit (AK-555, Enzo Life Sciences, Farmingdale, NY, USA) according to the manufacturer's instructions with some modifications. For experiments which examined the linearity of

enzyme activity at varying protein concentrations, rhSIRT1 (0–8 μg) was incubated for 30 min at 37°C with 25 μM *Fluor de Lys* SIRT1 substrate, which contained tetrapeptide comprising the amino acid sequence 379–382 of human p53 (Arg-His-Lys-Lys[ε-acetyl]), and 125 μM NAD^+ in a 0.5-mL tube. This reaction mixture was then transferred to a black, half-area, flat-bottomed well of a 96-well microplate (Corning 3694, Corning, NY, USA), and the same volume of Developer II in 2 mM nicotinamide was added to stop the reaction. The deacetylation-dependent fluorescent signal was then allowed to develop in the reaction mixture for an additional 45 min at 37°C. The fluorescence intensities were measured using a multi-label plate reader (Wallac 1420 ARVOSX, Perkin Elmer, Waltham, MA, USA; Ex. 355 nm, Em. 450 nm). Simultaneously, the reaction buffer was used instead of rhSIRT1 to compensate for the background fluorescence intensity. In experiments assessing the effect of small molecules on the SIRT1 enzyme activity, enzyme assays were performed as described above using rhSIRT1 (1 μg) in the presence of various concentrations (0–100 μM) of the test compounds or DMSO as a control.

Statistical analysis: *P* values were calculated from one-sample *t* test. $P < 0.05$ was considered to be statistically significant.

Acknowledgments - This work was partly supported by JSPS KAKENHI Grant Number JP16K08311 and the Research Institute of Meijo University.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8