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

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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