Introduction

Flavonoids are plant phenolic compounds that are widely distributed in foods and beverages [1]. They have been extensively studied with regard to their antioxidative and cytoprotective properties in various biological models [2-5]. They can protect against oxidative stress by scavenging reactive oxygen intermediates [6-8] and also by chelating iron [9]. Since oxidative damage to biomolecules, such as DNA and carbohydrate, proteins or polyunsaturated fatty acids is thought to play a significant role in mutagenesis, cancer, aging, and other human pathologies, considerable attention has been focused on the development of antioxidants to prevent or to treat diseases associated with oxidative stress [3, 10]. However, there is also some evidence that flavonoids themselves are mutagenic [11-14] and carcinogenic [15, 16] in both bacterial and mammalian experimental systems. The process that damages DNA, and is thus responsible for DNA alterations and genotoxicity, could be accelerated by the effects of metal ions, as naturally occurring metal constituents of the nucleus. Indeed, while quercetin is known to be a powerful antioxidant that scavenges free radicals associated with lipid peroxidation, the dietary administration of excessive quercetin has been reported to induce renal tubule adenomas and adenocarcinomas in male rats [15], as well as intestinal and bladder cancer in rats [16]. There is also considerable evidence that quercetin induces extensive DNA damage and forms 8-oxodG by reacting with Cu(II) [17]. Therefore, in order to develop an antioxidant for clinical use, a compound having a strong antioxidative activity but with a weak prooxidant effect has been desired.

Planar Catechin Analogue

Quercetin protects against oxidant injury and cell death [18] by scavenging free radicals [19, 20], thereby preventing lipid peroxidation [21] and terminating chain-radical reactions [22]. However, in the case of (+)-catechin (Cat), there have only been a few reports on this use for the treatment of free radical-associated disease, even though the mechanism of oxygen radical scavenging has been well studied [23, 24]. The superior antioxidant ability of quercetin results from the formation of a stable radical, due to the C2-C3 double bond and the resulting planar geometry which delocalizes the radical throughout the entire molecule [25]. Since the B ring in Cat is known to be a powerful antioxidant that scavenges free radicals associated with lipid peroxidation, the dietary administration of excessive quercetin has been reported to induce renal tubule adenomas and adenocarcinomas in male rats [15], as well as intestinal and bladder cancer in rats [16]. There is also considerable evidence that quercetin induces extensive DNA damage and forms 8-oxodG by reacting with Cu(II) [17]. Therefore, in order to develop an antioxidant for clinical use, a compound having a strong antioxidative activity but with a weak prooxidant effect has been desired.

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Antioxidative properties

The radical-scavenging activities of Cat and PC1 as well as that of quercetin were compared using the galvinoxyl radical (G•) as an oxyl radical species (Figure 2) [27]. Upon addition of Cat to a deaerated acetonitrile (MeCN) solution of G•, the absorption band at 428 nm due to G• disappeared immediately. This indicated that hydrogen abstraction from one of the OH groups on the B ring of Cat by G• had taken place to give the (+)-catechin radical and hydrogenated G• (GH). The decay of the absorbance at 428 nm due to G• disappeared immediately. This indicated that hydrogen abstraction from one of the OH groups on the B ring of Cat by G• had taken place to give the (+)-catechin radical and hydrogenated G• (GH). The decay of the absorbance at 428 nm due to G• obeyed pseudo-first-order kinetics when the concentration of Cat was maintained at more than 10-fold excess of the G• concentration. From the linear plot of the observed pseudo-first-order rate constant (kth) vs. the Cat concentration,
we determined that the second-order rate constant (k) for hydrogen abstraction of CA by G
was 2.34 \times 10^{3} \text{M}^{-1} \text{s}^{-1}. The k values for PC1 and quercetin were determined in the same manner to be 1.12 \times 10^{3} \text{M}^{-1} \text{s}^{-1} and 1.08 \times 10^{3} \text{M}^{-1} \text{s}^{-1}, respectively. Thus, the k values for PC1 and quercetin are about 5-fold larger than that for Cat. These results suggest that molecular planarity is essential for the radical-scavenging ability of antioxidants.

The hydroxyl radical is the most reactive oxygen-derived free radical and is responsible for aging and free radical-mediated injury. Therefore, the effects of Cat, PC1, and quercetin on hydroxyl radical-mediated DNA breakage were investigated. DNA-strand scission in supercoiled pBR322DNA was induced by a hydroxyl radical-generating system using hydrogen peroxide in the presence of Fe^{3+}/H_{2}O_{2}. Assays were performed in 50 mM sodium cacodylate buffer, pH 7.2, containing 45 \mu M of pBR322DNA, for 1h at 37°C. Lanes 1, 6, and 10; DNA alone, lanes 2, 7, and 11; 10 mM H_{2}O_{2} and 10 \mu M FeCl_{3}, lanes 3–5, 8 and 9, and 12–14; 10 mM H_{2}O_{2} and 10 \mu M FeCl_{3} in the presence of 0.25, 1.25, and 2.5 mM (+)-catechin (lanes 3–5), 0.25 and 1.25 mM quercetin (lanes 8 and 9), and 0.25, 1.25 and 2.5 mM PC1 (lanes 12–14).

**Radical scavenging mechanism**

Considering the radical scavenging mechanism of phenolic compounds, there are two possibilities in the mechanism of hydrogen transfer reactions: either a one-step hydrogen atom transfer or an electron transfer followed by proton transfer. We have recently reported that the hydrogen transfer from Cat to G or cumyloperoxy radical proceeds via electron transfer from Cat to G or cumyloperoxy radical [28]. This transfer is accelerated in the presence of metal ions such as Mg^{2+} or Sc^{3+}, followed by proton transfer. In such cases, the coordination of the metal ion to the one-electron reduced species of G or cumyloperoxy radical may stabilize the product, resulting in acceleration of the electron transfer process. On the other hand, the hydrogen transfer reaction of vitamin E proceeds via a one-step hydrogen atom transfer process, in this case there is no effect of metal ions on the hydrogen transfer rate from vitamin E to G [29–31]. Therefore, the effect of a metal ion on the rate of hydrogen transfer from PC1 to cumyloperoxy radical can distinguish between one-step hydrogen atom transfer and electron transfer mechanisms in the radical scavenging reaction of PC1.

The kinetics of hydrogen transfer from Cat and PC1 to cumyloperoxy radical has been examined in propionitrile (EtCN) at low temperature (203K) by use of ESR [32]. The photo irradiation of an oxygen-saturated EtCN solution containing di-butylylperoxide (BuOOCBu) and cumene with a 1000 W high-pressure mercury lamp results in formation of cumyloperoxy radical (PhCMe_{2}OO•), which was readily detected by a JEOL X-band spectrometer (JES-ME-1X). The cumyloperoxy radical is formed via a radical chain process shown in Figure 4. The photo irradiation of ‘BuOOCBu results in the homolytic cleavage of the O–O bond to produce ‘BuO’, which abstracts a hydrogen from cumene to give cumyl radical, followed by the facile addition of oxygen to cumyl radical. The cumyloperoxy radical can also abstract a hydrogen atom from cumene in the propagation step to yield cumene hydroperoxide, accompanied by regeneration of cumyl radical. When the light is cut off, the ESR signal intensity decays obeying second-order kinetics due to the bimolecular reaction. In the presence of PC1, however, the decay rate of cumyloperoxy radical after cutting off the light becomes much faster than that in the absence of PC1. The decay rate in the presence of PC1 (1.0 \times 10^{-4} M) obeys pseudo-first-order kinetics. This decay process is ascribed to hydrogen transfer from PC1 to cumyloperoxy radical (Figure 4). From the slope of the linear plot of k_{obs} vs concentration of PC1 is determined the second-order rate constant (k) for the hydrogen transfer from PC1 to cumyloperoxy radical as 9.7 \times 10^{5} \text{M}^{-1} \text{s}^{-1} in EtCN at 203K. The k value for Cat was also determined in the same
manner as $6.0 \times 10^2 \text{M}^{-1}\text{s}^{-1}$, showing that the hydrogen transfer rate from PC1 to cumyloperoxyl radical is significantly faster than that from Cat. By using this system, the effect of a metal ion on the $k$ value of PC1 was examined. As in the case of Cat, the hydrogen transfer from PC1 to cumyloperoxyl radical was significantly accelerated by the presence of Sc(OSO$_2$CF$_3$)$_3$ as shown in Figure 5. Thus, the hydrogen transfer from PC1 to cumyloperoxyl radical also proceeded via electron transfer from PC1 to cumyloperoxyl radical followed by proton transfer from PC1$^{2-}$ to one-electron reduced species cumyloperoxyl radical as shown in Figure 6.

**One-electron oxidation potential**

The larger $k$ value of PC1 as compared to that of Cat may be ascribed to the stability of the radical cation of PC1 (PC1$^{+}$), which is produced in the electron transfer from PC1 to cumyloperoxyl radical. The electron-donating $i$-propyl group at the B ring of PC1 may significantly stabilize PC1$^{+}$, resulting in the acceleration of the electron-transfer step. In such a case, the oxidation potential of PC1 is expected to be more negative than that of Cat. To determine the oxidation potential of PC1, the cyclic voltammogram of PC1 was recorded in MeCN containing 0.1 M TBAP as a supporting electrolyte at 298K. Two irreversible oxidation (anodic) peaks were observed at 1.22 V and 1.41 V vs SCE. A similar cyclic voltammogram was obtained for Cat, which exhibits irreversible oxidation peaks at 1.16 V and 1.35 V vs SCE. This indicates that the radical cation of Cat is too unstable at the time scale of CV measurements. The second-harmonic alternating current voltammetry (SHACV) method is known to provide a superior approach to directly evaluating one-electron redox potentials in the presence of follow-up chemical reaction, relative to the better-known DC and fundamental harmonic AC method, the SHACV method is applied to determine the oxidation potentials ($E^0_{ox}$) of PC1 and Cat in MeCN containing 0.1 M TBAP at 298K [40]. The $E^0_{ox}$ value of PC1 thus determined (1.01 V vs SCE) is significantly more negative than that of Cat (1.18 V vs SCE) as expected above [32]. Thus, PC1 may undergo one-electron oxidation by cumyloperoxyl radical more easily than Cat, showing excellent radical-scavenging ability.

**Reduced prooxidant property**

The antioxidant effects of flavonoids undoubtedly contribute to their chemopreventive activities. However, the fact that flavonoids themselves have antibacterial and bactericidal activities, as well as being mutagenic and pro-/co-carcinogenic, should be considered when contemplating their clinical use. Their harmful effects are thought to be due to their prooxidant activities. In the presence of Cu(II), Cat induces oxidative DNA damage and fatty acid peroxidation, due to production of reactive oxygen species via electron transfer from Cat to molecular oxygen mediated by Cu(II). However, this prooxidant effect is also observed for the dianion of Cat produced by the reaction between Cat and 2 equiv. of tetramethylammonium methoxide [33, 34]. The one electron-transfer reaction from dianion to molecular oxygen proceeds to form $O_2^\cdot$. The same reaction is also shown by the dianion (PC1$^{2-}$) of PC1, forming $O_2^\cdot$ by electron-transfer oxidation from PC1$^{2-}$ to $O_2$ as confirmed by a JEOL X-band spectrometer (JES-FA100) [35]. A characteristic ESR $g_{uv}$ value of 2.070 due to $O_2^\cdot$, together with an ESR $g_{uv}$ value of 2.050 for protonated $O_2^\cdot$ (HO$_2^\cdot$) was observed for an $O_2$-saturated MeCN solution of PC1 and 2 equiv. of methoxide (MeO$^-$) at 77K, as shown in Figure 7b. During $O_2^\cdot$ generation, the resultant radical anion from PC1 underwent an intramolecular proton transfer to give an o-semiquinone radical anion form (PC1$^{+}$), with a characteristic ESR $g$ value of 2.0048 at 298K, as shown in Figure 7a.

If one molecule of PC1$^{2-}$ reacts with one molecule of $O_2$, the rate of electron transfer from PC1$^{2-}$ to molecular oxygen should show first-order dependence. In fact, the increase in absorbance at 485 nm due to the radical anion of PC1 obeyed pseudo-first-order kinetics under conditions where the $O_2$ concentration was maintained at more than 10-fold excess relative to the PC1$^{2-}$ concentration. The $k_{obs}$ increases linearly with increases in $O_2$ concentration. The slope of
the linear plot of $k_{obs}$ vs. $[O_2]$ gave the second-order rate constant of the electron transfer ($k_\alpha$) from PC1$^{2-}$ to $O_2$: $2.8 \times 10^{-5}$ M$^{-1}$s$^{-1}$. This $k_\alpha$ value is about half of that determined for Cat (5.8 $\times$ 10$^{-5}$ M$^{-1}$s$^{-1}$), indicating that electron transfer from PC1$^{2-}$ to $O_2$ proceeds slower than from Cat. While PC1 provides efficient protection against DNA strand breakage induced by Fenton reaction, the low $k_\alpha$ value implies that, in physiologically relevant systems, the ability of PC1 to generate oxygen radicals responsible for its prooxidant activity might not be as high as that of Cat. Among natural antioxidants, α-tocopherol and ascorbic acid are typical compounds which are useful for the treatment or prevention of diseases associated with oxidative stress. However, administrating a large amount of such antioxidants is unfavorable because of their prooxidant properties, similarly to Cat or quercetin. Therefore, the use of PC1, rather than natural antioxidants such as Cat, quercetin, α-tocopherol, ascorbic acid, etc., might be favorable for the treatment of diseases associated with oxidative stress due to suppression of oxidant injury as a side-effect arising from the antioxidant itself.

**Biological properties**

In addition to antioxidant ability, catechin is known to have several biological activities, including anti-allergic effects, inhibition of α-glucosidase, antibacterial, antiviral, and antitumor activities, though none of these activities are particularly strong. Therefore, the inhibitory effects of PC1 on α-glucosidase from *Saccharomyces cerevisiae* and *Bacillus stearothermophilus* were evaluated [36]. Surprisingly, in contrast to the relative weak inhibitory effect of catechin with an IC$_{50}$ $>$ 500 µM, PC1 exhibited strong inhibitory effects of the respective α–glycosidases with IC$_{50}$ = 1.2 µM (*S. cerevisiae*) and 0.7 µM (*B. stearothermophilus*). As α–glycosidase catalyzes the final step in the digestive process of carbohydrates, the strong inhibitory effect on α–glycosidase suggested that PC1 may be used as a lead compound for the development of antidiabetic therapeutics, similar to Acarbose and Voglibose which are known to reduce postprandial hyperglycemia primarily by interfering with carbohydrate digesting enzymes and delaying glucose absorption.

Potent antiviral activity of PC1 was also shown by significant inhibition of Newcastle Disease Virus infection of BHK cells [36]. Considering the strong inhibitory effect on α–glucosidase, the antiviral activity of PC1 may be attributed to inhibition of α–glucosidase during protein synthesis that is essential for virus proliferation [37].

### Methyl Resveratrol

**Resveratrol**

Resveratrol (3',4',5,4'-trihydroxy-trans-stilbenetran-3,4'-5-hydroxystilbene) is a natural phytalexin present in grapes and wine, which that has been shown to play an essential role in the prevention of several human pathological processes including, such as inflammation [38], atherosclerosis [39] and carcinogenesis [40]. The cancer preventive activity of resveratrol is linked to its ability to eliminate free radicals and to reduce oxidative and mutagenic stress. It has been demonstrated that resveratrol suppresses lipid peroxidation by both scavenging of the free radicals and chelation of copper [41]. Among three hydroxyl groups in resveratrol, and 4'-hydroxyl group is essential for radical-scavenging activities [42–44]. Besides, 4'-hydroxyl group has been primarily responsible for copper binding property [45]. In addition to the meritorious benefits effectual, resveratrol is genotoxic, inducing a high frequency of chromosomal aberrations (CA), micronucleus, and sister chromatid exchanges (SCE) in vitro [46]. SCE is induced during DNA replication, and the formation is a result of homologous recombination. As shown in Figure 8, resveratrol is a potent inducer of SCE.

In this regard, we have shown that resveratrol is able to mediate Cu(II)-dependent DNA strand scission under neutral conditions [47]. It has also been shown that DNA cleavage is more likely caused by a copper-peroxo complex as the reactive species rather than by a freely diffusible oxygen species. However, the structural feature of resveratrol that is effective for DNA cleavage is still unknown. We have then designed to explore the substrate specificity of synthesized hydroxystilbene derivatives for Cu(II) and DNA binding [48]. To confirm the electrostatic interaction of hydroxylated stilbene with both Cu(II) and DNA, ESR signals of Cu(II) were observed in the presence of resveratrol or its analogues together with calf thymus DNA by using a JEOL X-band spectrometer (JES-FE 2XG). Once the ternary complex of Cu(II)-resveratrol-DNA, which is due to the efficient binding affinities of resveratrol with both Cu(II) and DNA, is formed, the complex may result due to its high DNA-cleaving ability.
9 shows that an ESR signal of Cu(II) became insufficient binding affinity of 
with both of isoresveratrol (complex was not observed with the addition 
reduction of the peak height of Cu(II)-DNA 
Cu(II) to Cu(I) by resveratrol, an efficient 
analogues. Compared to the reduction of 
that Cu(II) remains in a complex with DNA 
for other resveratrol analogues, suggesting 
increase in peak height was also not observed 
increase to the height of unbound Cu(II). An 
resveratrol, the signal of Cu(II) should 
Cu(II) to DNA decreases with the addition of 
plex and thus induced the reduction of Cu(II), 
resveratrol was bound to Cu(II)-DNA com-
the resonance was weakened, suggesting that 
-half of that of the Cu(II)-DNA complex and 
height of the ESR signal was reduced to one-
solution of Cu(II)-DNA complex, the peak 
of Cu(II). When resveratrol was added to the 
molecule of DNA, which limits the mobility 
Cu(II) in a solution of calf thymus DNA is 
tent with the fact that Cu(II) complexes DNA. 
multiple upon the addition of DNA, consis-
titive effects on the aromatic ring [29]. In par-
ticularly, methyl groups at the ortho position to 
hyperconjugation. In this study, we describe 
resveratrol analogues where methyl groups 
are introduced into the ortho position of 4'-hydroxyl group as shown in Figure 10 [49]. 
Methyl groups were also introduced at the 4' 
position para to the 4'-hydroxy group. These 
designed methyl derivatives (11 and 12) of 
resveratrol, 4-methylresveratrol (13) and its 
ethyl derivatives (14 and 15) were synthe-
sized by means of Wittig-Horner reactions 
between appropriate dibenzyloxybenzylphos-
loxybenzaldhydes (3, 4, 5), followed by 
deprotection using AlCl3 and N,N-dimethyl-
aniline. Trans geometries of these compo-
unds were confirmed by their coupling constants (16.0–16.4 Hz) for the olefinic pro-
Effect on the antioxidative property

The radical scavenging activities of resvera-
trol and its analogues were evaluated by the 
hydrogen transfer reaction using G• as an oxy-
radical species [49]. The hydrogen abstraction 
from resveratrols by G• in deaerated MeCN 
was monitored the decrease of absorbance at 
428 nm due to G’ that obeyed pseudo-first-

**Fig. 9** Effect of resveratrol and its analogues on the ESR spec-
tra of Cu(II) in the presence of calf thymus DNA. 
Spectra A is CuCl2 and spectra B-F show after addition 
of 2 mM nucleotide phosphate of calf thymus DNA in 
the absence (B) or presence of 1 mM chemicals (C: 
resveratrol; D: d; E: e; F: f). All spectra were recorded 
after incubation for 30 min at room temperature.

**Fig. 10** Synthesis of methyl analogues of resveratrol.

- Structure-activity relationship studies of resveratrol analogues revealed that the 4'-hydroxyl group, besides being essential for antioxidative activity, is also responsible for the in vitro cytogenetic activity of resveratrol [45, 48]. In this regard, our challenge is to design novel resveratrol analogues that not only exert enhanced antioxidative abilities but also have reduced in vitro genotoxicity. Such analogues could lead to the development of new drugs against various diseases, particularly those related to oxidative stress.

- In our attempt to design new resveratrol analogues, we focused on the methyl groups of the tocopherol due to their proven antioxidative effects on the aromatic ring [29]. In particular, methyl groups at the ortho position to the hydroxyl group contribute to delocalization of the unpaired electron of the corre-
- syndrome deprotection using AlCl3 and 

- ![Resveratrol Structure](image)

- ![Methyl Resveratrol Analogue Synthesis](image)
order kinetics, when the concentration of resveratrol was maintained at more than a 10-fold excess of the \( G^* \) concentration. The second-order rate constant \((k)\) for hydrogen abstraction was determined from the linear plot of pseudo-first-order rate constant vs the resveratrol concentration. 3'-Methylresveratrol (11), where one methyl group was introduced at the ortho position relative to the 4'-hydroxyl group, showed a significantly increased radical scavenging activity compared to resveratrol. A greater \( k \) value was also obtained in compound 12, which has methyl groups at both positions ortho to 4'-hydroxyl group. In comparison to resveratrol, a 6-fold greater \( k \) value was observed with 4-methylresveratrol (13), indicating that the 4-methyl group also affects the radical scavenging activities of the 4'-hydroxyl group. Similar to the methyl analogues (11 and 12) of resveratrol, the \( k \) value of 13 was increased by the introduction of methyl ortho to the 4'-hydroxyl group. Among resveratrol and its derivatives, compound 15 had the strongest antioxidative activity with a 60-fold greater \( k \) value than that of resveratrol.

In order to verify that the ortho-methyl group contributes to delocalization of the unpaired electron in the corresponding phenoxy radical, the ESR spectrum was measured for a solution containing 15 and \( G^* \) by a JEOL X-band spectrometer (JES-FA100) as shown in Figure 11a. The observed ESR signals were characterized as the phenoxy radical derived from 15 by computer simulation with the hyperfine splitting (hfs) values \((a_{CH3} = 0.141 \text{ mT}, a_{H} = 0.601 \text{ mT})\) as shown in Figure 11b. We clearly demonstrated that the delocalization of the unpaired electron to the ortho-methyl groups by hyperconjugation results in the stronger antioxidative ability of ortho-methyl derivatives as compared to resveratrol.

**Effect on the genotoxicity**

We next considered the effect of the ortho-methyl group on genotoxicity of resveratrol by means of the frequency of CA [49]. Chinese hamster lung (CHL) cells were incubated with resveratrol and its analogues for 48 h, and the number of cells with structural CAs was counted after chromosome preparation. Figure 12a is a typical result of CA tests and
the frequency of CA is summarized in Figure 12b. In agreement with a previous report, resveratrol induced a high frequency of CA consisting of obvious chromatid gaps and chromatid breaks. 4-Methylresveratrol (13) showed a slightly higher frequency of CA compared to resveratrol. Remarkably, o-methyl groups relative to 4'-hydroxy group resulted in reduced genotoxicity. In the case of 15, chromosomes were almost normal as shown in Figure 12a. It is noteworthy that the frequency of CA induced by 11 and 14 was low, whilst CA induced by 12 and 15 was almost insignificant. These results suggest that two methyl substitutions reduce CA even more significantly than a single methyl substitution.

Conclusion

The primary goal of this project was to develop a novel antioxidant, with potential for clinical usage and/or chemoprevention of diseases associated with reactive oxygen species. The planar catechin analogue that we synthesized from Cat was constrained to be planar compared with the structure of Cat, by taking advantage of the formation of a bridge between the 3-OH group on ring C and C6' on ring B. As compared with Cat, PC1 showed strong radical scavenging activities towards both galvinoxyl radicals and cumyloxyl radicals. The O2•− generating ability of the diol form of PC1 was much lower than that of Cat, suggesting that PC1 may be a promising novel antioxidant with reduced prooxidant activity. In fact, PC1 inhibited DNA-strand scission induced by the Fenton reaction efficiently, whereas Cat exhibited not only antioxidant properties in the same reaction but also prooxidant properties consistent with enhanced DNA strand cleavage. The prevention of polyphenols toward coronary diseases and cancer is due to antioxidant properties of polyphenols which should rely, at least in part, on their ability to inhibit lipid peroxidation in plasma low-density lipoproteins (LDL). The proper lipophilicity of PC1 owing to its molecular planarity might be favorable for its antioxidant effect into LDL or cell membrane. If the hydrophobicity of PC1 could be controlled so as to fine-tune its membrane binding and penetration into the phospholipid bilayer, PC1 might be valuable in the development of a new type of clinically useful antioxidant. Therefore the synthesis of planar catechin analogues, the lipophilicity of which is controlled by changing the length of the alkyll chains instead of methyl group in PC1 and their antioxidant abilities are currently underway in our laboratories [50].

We have also described the synthesis, antioxidative ability and genotoxicity of resveratrol analogues with methyl groups ortho to the 4'-hydroxy group. We demonstrated that the oxidative activity coupled with reduced genotoxicity, rendering the methyl analogues 11–15 potentially valuable for development of drugs effective for various types of diseases caused by oxidative stress. The genotoxicity of resveratrol has been attributed to scavenging of tyrosyl free radicals in the R2 subunit of ribonucleotide reductase that catalyzes the rate limiting step of de novo DNA synthesis [51]. We previously reported that the 4'-hydroxy group is responsible for scavenging tyrosyl radicals, which cause SCE and CA [52]. Therefore, it is possible that the lower CA frequency for 11–15 as compared to resveratrol could be explained by the steric hindrance of the o-methyl group with respect to the radical scavenging reaction between the 4'-hydroxy group and the tyrosyl radical. Comparison of resveratrol and its o-methyl analogue (11 and 12) to the 4-methyl analogues (13–15), which have increased CA, shows a potential functional relationship between structure and enhanced radical scavenging activity. Further detailed insight and in vivo studies to fully exploit these potential benefits are currently underway.

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