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RESEARCH ARTICLE

# A novel salvianolic acid A analog with resveratrol structure and its antioxidant activities in vitro and in vivo

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## Abstract

E-DRS is a novel salvianolic acid A (SAA) analog, which was synthesized from resveratrol (RES) and methyldopate. Its structure is similar to that of SAA, but the 3′,4′-dihydroxy-*trans*-stilbene group and the ester structure in SAA were replaced by the RES structure and an amine group, respectively. E-DRS scavenged free oxygen radicals effectively, including superoxide anion (ascorbic acid > E-DRS > SAA ≥ rutin > RES) and DPPH radical (rutin > E-DRS ≥ ascorbic acid > SAA > RES), and exhibited powerful total antioxidant capacity (ascorbic acid > E-DRS > SAA ≥ rutin > RES) in vitro. Furthermore, oral administration of E-DRS dose-dependently and significantly decreased $CCl_4$-induced oxidative stress in mice as indicated by the decreased content of hepatic malondialdehyde (MDA). In addition, oral administration of E-DRS also increased the content of nonenzymatic antioxidant glutathione (GSH) and the activity of antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD) in the liver of mice. All these results demonstrated that E-DRS had good antioxidant activities both in vitro and in vivo, and could be a potential antioxidant agent after further optimization and evaluation.

KEYWORDS

antioxidant, free radical scavenging ability, resveratrol, salvianolic acid A

## 1 | INTRODUCTION

Free radicals, like reactive oxygen species (ROS), which contain one or more unpaired electrons in their outer orbital, are short-lived and highly chemically reactive and have long been considered harmful molecules although recent studies demonstrated they also play important roles in some physiological reactions (Szewczyk-Golec, Czuczejko, Tylzanowski, & Lecka, 2018). An excessive amount of free radicals can damage sensitive tissues directly and has been implicated in a variety of pathological events, such as neurodegenerative diseases (Wojtunik-Kulesza, Oniszczuk, Oniszczuk, & Waksmundzka-Hajnos, 2016), myocardial infarction (Rezvan, 2017; Zhou et al., 2019), cancer (Katerji, Filippova, & Duerksen-Hughes, 2019), etc. The term oxidative stress has been proposed indicating a serious imbalance between the production of ROS and cellular antioxidant capacity. Both enzymes, like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase-1 (GPx-1), and nonenzymatic antioxidants, like reduced glutathione (GSH), comprise a co-operative network to minimize oxidative injury (Marengo et al., 2016; Xie, Liu, & Bian, 2016). High intake of natural antioxidant-rich food, like plant polyphenols, has been proved to reduce the risk of oxidative stress-related diseases (Sarubbo, Moranta, & Pani, 2018; Teixeira et al., 2019; Zhang, 2015).

Resveratrol (RES) is a natural *trans*-stilbene compound derived from the peel of several plants, including grapes, berries, and pomegranates. It attracted little interest until the 1990s when it was found rich in red wine and was to postulate as a possible explanation for the paradoxical epidemiological finding that French people have a relatively low incidence of cardiovascular disease despite a high saturated fat diet (Bertelli et al., 1995; Chung, Teng, Cheng, Ko, & Lin, 1992).

During the last two decades, growth studies dealing with the biological activity of RES have been carried out and RES was shown numerous health-promoting effects in both animals and humans (Lopez, Dempsey, & Vemuganti, 2015). In several studies, RES, like other polyphenolic compounds, displayed a potent ability to scavenge free radicals, and the antioxidant capacity of RES was thought to be essential for its biological effects (Bonnefont-Rousselot, 2016; Santos, de Carvaho, Oliveira, Raposo, & da Silva, 2013; Truong, Jun, & Jeong, 2018). However, the low bioavailability and stability of RES make it worthwhile to develop newer derivatives or analogs to improve its pharmacological activities.

Salvianolic acid A (SAA) is one of the main water-soluble polyphenol compound extracted from the dried roots and rhizomes of *Salvia miltiorrhiza*. It has been shown to reduce oxidative stress and exerts a broad range of protective effects on hepatic fibrosis (Wang et al., 2019), ischemia–reperfusion injury (Hou et al., 2016), Alzheimer's disease (Zhang, Qian, Zhang, & Wang, 2016), etc. Although SAA has recently attracted many interests, the low abundance of SAA in the raw material (<0.05% content in the roots of *Salvia miltiorrhiza* [Xu et al., 2018]) prevents it from being used widely in clinic trials, and few follow-up studies of SAA have been carried out because of two serious reasons. First, the complex structure of SAA means that more expensive and complex synthesis methods are needed, and a new method for the total asymmetric synthesis of SAA was reported till 2016 (8 steps, overall yield <10%) (Zheng, Song, & Xuan, 2016). Second, SAA could be hydrolyzed in vivo due to the ester bond, which reduces its pharmacological activity. Recently, Tang et al. (2016) replaced the C-9 ester bond of salvianolic acid C with amide linkage to develop a series of analogs. They found that the *ortho*-phenol hydroxyl group of these derivatives is essential to maintain their antioxidant properties, which were further enhanced by the replacement of amide linkage. It is also worth noting that the scaffolds of salvianolic acid are retained in these derivatives.

As SAA could be regarded as the ester of phenylpropionate and *trans*-stilbene, if the *trans*-stilbene group in SAA is substituted by similar *trans*-stilbene structure and the amine structure is used as the linkage instead of the ester structure, the SAA analog might show more stability and more effective antioxidant potency. Herein, we design and synthesis a kind of SAA analog, E-DRS. Its structure is similar to that of SAA, but RES structure was substituted for the 3′,4′-dihydroxy-*trans*-stilbene group and an amine group was used as the linkage instead of the ester structure of SAA. In addition, its antioxidant activity was further investigated in vitro and in vivo.

## 2 | MATERIALS AND METHODS

### 2.1 | Chemistry

RES (98%), methyldopa, SAA (99.5%), rutin, and ascorbic acid are products of Sigma-Aldrich and were purchased from Maike Biological Reagent Company (Changsha, China). Other chemicals were of analytical grade from commercial sources.

### 2.2 | General procedure for the synthesis of E-DRS (compound IV)

One gram RES (compound **I**, 4.4 mmol) was dissolved in 5 ml of N,N-dimethylformamide (DMF) and 7.5 ml of Vilsmeier regent ($POCl_3$ mixed with DMF 1:2) was added slowly to it with an ice/water bath. The reaction mixture was stirred for 1 hr at room temperature, and another 30 ml of ice-water was added slowly to make sure the temperature was below 60 °C, otherwise, the solution will turn black. An additional 50 ml of water was added until suspended yellow solids appear and stir the yellow solution overnight. Resveratrol aldehyde ((E)-2,4-dihydroxy-6-(4-hydroxystyryl)-benzaldehyde, compound **II**) was obtained by filtration and vacuum drying at 80 °C (95% yield) (Huang et al., 2007; Kataria & Khatkar, 2019).

For the preparation of ethyl methyldopate, the dry hydrogen chloride gas was bubbled into 3.3 g methyldopa (15.6 mmol) solution suspended in 30 ml of ethanol, then stirred, heated, and refluxed for 4–8 hr, and the excess solvent was removed by vacuum distillation (90% yield).

To get compound **III**, 0.3 g (1 mmol) resveratrol aldehyde (compound **II**) and 0.5 ml (1.6 mmol) ethyl methyldopate were dissolved in 20 ml of methanol, and then the solution was heated to reflux for 3 hr. After cooling, the reaction mixture was poured into 50 ml of water. The aqueous layer was extracted with ethyl acetate (3 × 20 ml), and the organic layer was dried with sodium sulfate and vacuum drying. Compound **III** was obtained when the crude product was further purified by column chromatography (eluent = dichloromethane: methanol = 30:1) (50 ∼ 90% yield).

Finally, 0.2 g (0.4 mmol) compound **III** was dissolved in 20 ml of methanol at room temperature, and then 0.04 g solid $NaBH_4$ was added carefully. After stirring for 1 hr, the solution was poured into 50 ml of water, and the aqueous layer was extracted with ethyl acetate (3 × 20 ml). Compound **IV** (the title compound) was finally obtained by drying the organic layer with sodium sulfate and vacuum drying (90% yield).

Compound **IV** is a yellowish powder, $^1$H NMR (400 MHz, MeOD) $\delta$ 7.78 (d, $J$ = 8 Hz, $^2$H), 7.62 (d, $J$ = 8 Hz, $^1$H), $\delta$ 7.46 (m, $^3$H), $\delta$ 7.24 (d, $J$ = 4 Hz, $^1$H), $\delta$ 7.19 (d, $J$ = 8 Hz, $^1$H), $\delta$ 7.16 (d, –CH=CH–, $^1$H), $\delta$ 6.57 (d,–CH=CH–, $^1$H), $\delta$ 6.36 (s, $^1$H), $\delta$ 6.25 (s, $^1$H), $\delta$ 4.15–4.11 (t, $^2$H), $\delta$ 4.00–3.95 (t, $^2$H), $\delta$ 2.56(s, $^2$H), $\delta$ 2.16 (s, $^3$H), $\delta$ 1.76–1.82 (t, $^3$H). $^{13}$C NMR (101 MHz, MeOD) $\delta$ 158.22, 156.92, 139.95, 129.03, 128.04, 127.45, 125.61, 115.12, 104.44, 101.27, 48.31, 48.10, 47.89, 47.67, 47.46, 47.25, 47.04. MS (ESI): $m/z$ Calcd. For $C_{27}H_{29}NO_7$ $[M + H]^+$: 479.195; found: 479.333. IR (KBr, 1 mg) $\nu_{max}$: 3459, 3340, 1586, 1608, 1516, 1276, 1173, 977, 811 $cm^{-1}$.

### 2.3 | Antioxidant activity assessment in vitro

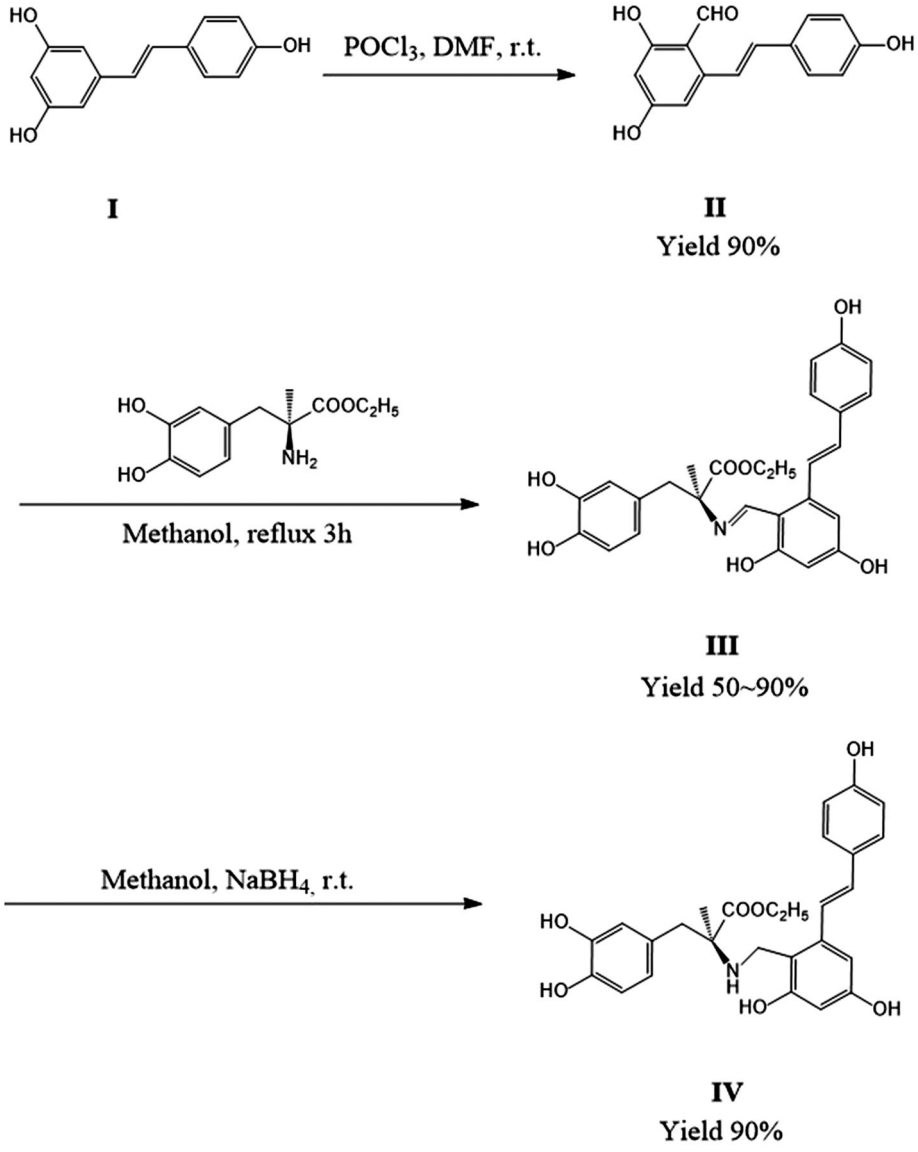
#### 2.3.1 | Total antioxidant capacity

The total antioxidant capacity of E-DRS was measured by Ferric ion reducing antioxidant power (FRAP) assay using a FRAP assay kit (Cat

No. S0116, Beyotime Biotechnology, Shanghai, China) according to the manufacturer's instructions. Simply, samples were mixed with fresh $Fe^{3+}$-TPTZ (Ferric-tripyridyltriazine) working solution and incubated at 37 °C for 40 min in dark. Then the absorbance of each sample was measured at 593 nm with a spectrophotometric plate reader (BioTek, Winooski, VT). Deionized water instead of the sample was used as a blank. Each sample was assayed at least three times.

### 2.3.2 | Superoxide anion scavenging activity

The pyrogallol autoxidation method was carried out to determine superoxide free radical scavenging ability of E-DRS as described previously with slight modifications (Li, 2012). Briefly, 200 μl sample was mixed with 2,750 μl of Tris–HCl buffer (0.05 M, containing 1 mM $Na_2EDTA$, pH 8.2) and 50 μl of pyrogallol solution (60 mM in 1 mM




**SCHEME 1** Synthetic routes for E-DRS (title compound)

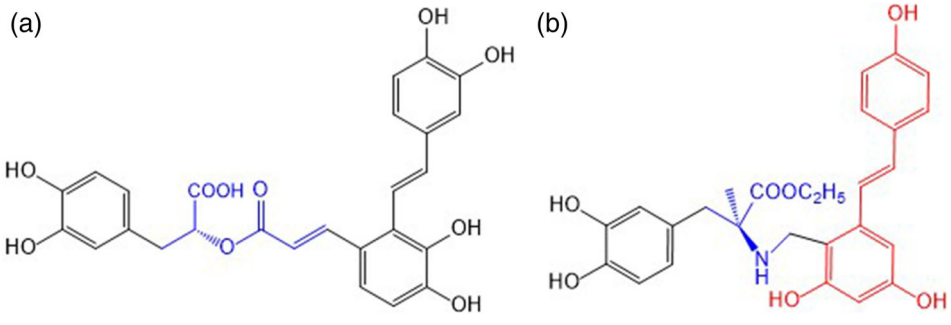



**FIGURE 1** Chemical structure of salvianolic acid A (a) and E-DRS (b)

HCl, 37 °C), vibrated with a vortex for several seconds, and then send to the spectrophotometric plate reader quickly to monitor its absorbance at 325 nm every 30 s for 5 min. The superoxide free radical scavenging ability was calculated using the following equation:

$$\text{Scavenging ability}(\%) = \left\{\left(\Delta A_{325,\text{control}} - \Delta A_{325,\text{sample}}\right)/\Delta A_{325,\text{control}}\right\} \times 100.$$

Here, $\Delta A_{325,\text{control}}$ is the increase of absorbance at 325 nm in 5 min of the mixture without the sample and $\Delta A_{325,\text{sample}}$ is that of the mixture with the sample. The concentration of each sample decreasing 50% of scavenging ability ($IC_{50}$) was used to measure the superoxide anion scavenging activity level. The assay was repeated a minimum of three times.

### 2.3.3 | DPPH radical scavenging activity

The scavenging activity of E-DRS on 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals was performed as described previously with minor modifications (Shimamura et al., 2014). Briefly, 200 μl of increasing concentration of sample solution (7.8, 15.6, 31.3, 62.5, 125, 250, 500 μg/ml), 800 μl of 0.1 M Tris–HCl buffer (pH 7.4), and 1 ml of 0.2 mM DPPH-ethanol solution was added into a test tube and mixed for 10 s quickly. The reaction mixture was then incubated for 30 min at room temperature in the dark. 200 μl of ethanol instead of the sample was used as blank control. The absorbance was measured at 517 nm, and the inhibition ratio was calculated using the following equation:

$$\text{Inhibition ratio}(\%) = \left\{\left(A_{\text{con}} - A_{\text{sample}}\right)/A_{\text{con}}\right\} \times 100.$$

Here, $A_{\text{sample}}$ represents the absorbance of the sample group, while $A_{\text{con}}$ represents the absorbance of the control group. $IC_{50}$ was used to measure the DPPH scavenging activity level. Each sample was assayed at least three times.

## 2.4 | Antioxidant activity assessment in vivo

### 2.4.1 | Animal experiment

The animal research protocol was approved by the animal ethics committee of the University of South China. After institutional ethical clearance for the study was acquired, 70 Kunming male mice weighing 20–25 g were purchased from the Laboratory Animal Centere of University of South China (Certificate No. SCXK 2015-0002). The mice were housed under standard environmental conditions (22 ± 2 °C, 12 hr light, and 12 hr dark cycle) and fed a standard commercial pellet diet and water ad libitum. The animals were acclimatized for 1 week and then randomly divided into 7 groups with 10 animals each. Vit C and RES were used as positive control drugs for economic reasons. Mice were pre-treated with E-DRS (5, 25, or 125 mg/kg body weight), ascorbic acid (7.5 mg/kg body weight), RES (25 mg/kg body weight), or the same volume of saline (0.5 ml, $n$ = 20, 10 mice for the blank control group, and 10 mice for injured model group induced by $CCl_4$) by intragastric gavage for 14 days. Two hours after the last dosing, mice except that of blank control group were injected with 5% $CCl_4$ (dissolved in olive oil, 6 ml/kg body weight) intraperitoneally to induce higher levels of oxidative stress, while the mice in the blank control

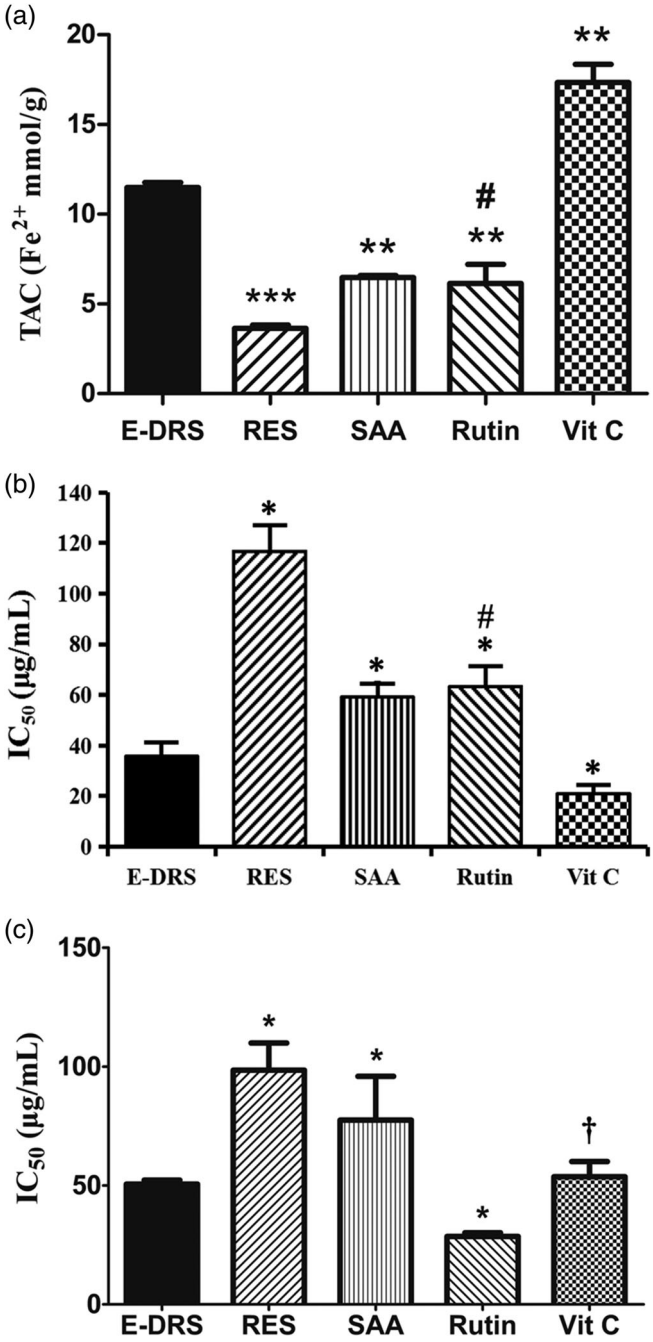



**FIGURE 2** Antioxidant activities of E-DRS in vitro (a) Total antioxidant capacity (TAC) of E-DRS measured by the FRAP method. All compounds were prepared at the same test concentration of 0.125 mg/ml. (b,c) Superoxide anion scavenging ability (b) and DPPH radical scavenging activity (c) are reported in terms of $IC_{50}$ (μmol). Data are expressed as mean ± S.E.M. ($n$ = 9 from 3 separate experiments), $^{**}p < .01$, $^{***}p < .001$ versus E-DRS group, $^{\#}p > .05$ versus SAA group, $^{\dagger}p > .05$ versus E-DRS group

group were injected with an equal volume of olive oil. Two hours later, all mice were allowed to drink water ad libitum but fasted strictly.

Twenty four hours after the last treatment, mice were all anesthetized using diethyl ether. Then liver tissues were removed and washed with ice-cold saline immediately. About 0.2 g liver were homogenized with the corresponding buffer according to the protocols of commercially available kits. The tissue lysates were centrifuged at 2,500 rpm for 20 min at 4 °C, and the supernatant was used for assaying the levels of MDA, CAT, SOD, and GSH following the manufacturer's instructions.

### 2.5 | Statistical analysis

All experiments were repeated at least three times, and results were expressed as the means ± S.E.M. Statistical analysis was performed using one-way ANOVA and comparisons between means were carried out according to Bonferroni post hoc test. $p < .05$ was considered statistically significant.

## 3 | RESULTS AND DISCUSSION

### 3.1 | Chemistry (structure elucidation)

The synthesis of E-DRS, a kind of SAA analog, was accomplished by esterification, acylation, and aldimine condensing reaction according to the pathway illustrated in Scheme 1. Compound **II** was synthesized from RES (compound **I**) via Vilsmeier formylation reaction according to the report previously (Huang et al., 2007; Kataria & Khatkar, 2019). It was then condensed with methyldopa in methanol to form the Schiff bases (compound **III**), which was further purified by column chromatography. Finally, compound **III** was reduced by NaBH4, and a more stable saturated alkylamine (compound **IV**) was obtained.

### 3.2 | Antioxidant activities of E-DRS in vitro

At first, we used the DPPH method to measure the free radical scavenging activity of compounds **III** and **IV**, in order to explore the relationship between the imine moiety and its antioxidant activity preliminarily. Our result showed that the scavenging efficiency improved nearly threefold from average 25.7–66.7% when the C-N double bond in compound **III** was reduced to the C–N single bond in compound **IV**. Compound **IV** was then used throughout this study and named E-DRS. Figure 1 shows the chemical structure and differences between E-DRS and SAA.

Next, the total antioxidant capacity (TAC) and free radical (including $\bullet O_2^-$ and DPPH•) scavenging ability experiments were used to compare the antioxidant activities of E-DRS, RES, and SAA in vitro. Rutin and ascorbic acid (Vit C) were used as positive control antioxidants throughout this study. The results are shown in Figure 2.

According to the TAC assay, all compounds exerted good antioxidant activity at the same test concentration (0.125 mg/ml). The effect of E-DRS is weaker than that of Vit C but stronger than that of rutin, SAA, and RES significantly (all $p < .01$). The relative antioxidant capacities of the compounds were in the order: Vit C > E-DRS > SAA ≥ rutin > RES (Figure 2(a)).

According to the pyrogallol autoxidation method, the superoxide anion scavenging ability of E-DRS was also obviously higher than that of RES, SAA, and rutin, but weaker than that of Vit C (all $p < .05$). The mean $IC_{50}$ value for E-DRS was 35.79 ± 5.40 μg/ml, which is approximately 1.5-fold more potent than that for SAA (59.12 ± 5.38 μg/ml) and rutin (63.17 ± 7.97 μg/ml) and approximately threefold more potent than RES (116.7 ± 10.36 μg/ml). The relative potency of the compounds was in the order: Vit C > E-DRS > SAA ≥ rutin > RES (Figure 2(b)).

In the DPPH assay, the free radical scavenging ability of E-DRS is similar to that of Vit C, higher than that of RES and SAA, but weaker than that of rutin. The relative potency of the compounds was in the order: rutin > E-DRS ≥ Vit C > SAA > RES (Figure 2(c)).

All these results demonstrated clearly that E-DRS has considerable antioxidant activities in vitro.

### 3.3 | Hepatoprotective activity of E-DRS

Intraperitoneal administration of carbon tetrachloride ($CCl_4$) is a classic method to induce free radical generation. It had been extensively used for the evaluation of antioxidant agents in vivo (Li et al., 2016).

**TABLE 1** Effects of E-DRS on hepatic MDA, GSH contents, and CAT and SOD-like activities in $CCl_4$-treated mice

| Group | MDA[a] (nmol/mg protein) | GSH[a] (U/g protein) | CAT[a] (U/g protein) | SOD[a] (U/g protein) |
|---|---|---|---|---|
| Control | 0.083 ± 0.002 | 14.82 ± 0.62 | 852.2 ± 26.87 | 21.97 ± 1.14 |
| Model | 0.103 ± 0.002$^{\#\#}$ | 8.12 ± 0.26$^{\#\#}$ | 724.2 ± 53.53$^{\#\#}$ | 10.24 ± 0.66$^{\#\#}$ |
| E-DRS$_L$[b] | 0.091 ± 0.001$^{**}$ | 9.49 ± 0.69$^{**}$ | 783.3 ± 21.86$^{**}$ | 13.37 ± 1.65$^{**}$ |
| E-DRS$_M$[b] | 0.083 ± 0.002$^{**}$ | 10.86 ± 0.64$^{**}$ | 809.0 ± 12.14$^{**}$ | 13.58 ± 1.75$^{**}$ |
| E-DRS$_H$[b] | 0.081 ± 0.005$^{**}$ | 12.88 ± 0.75$^{**}$ | 875.0 ± 18.03$^{**}$ | 18.26 ± 1.05$^{**}$ |
| Vit C | 0.092 ± 0.001$^{**,\dagger}$ | 9.06 ± 0.68$^{*,\dagger}$ | 762.3 ± 41.37$^{**,\dagger}$ | 12.90 ± 0.86$^{**,\dagger}$ |
| RES | 0.082 ± 0.001$^{**}$ | 10.01 ± 0.62$^{**,\dagger}$ | 829.5 ± 9.7$^{**,\dagger}$ | 15.65 ± 0.81$^{**,\dagger}$ |

[a]Data are expressed as mean ± S.E.M., $n = 10$. $^{\#\#}p < .01$ versus control group, $^{*}p < .05$, $^{**}p < .01$ versus model group, $^{\dagger}p < .05$ versus E-DRS$_H$ group.
[b]E-DRS$_L$, E-DRS$_M$, and E-DRS$_H$ represent 5, 25, or 125 mg/kg day of E-DRS *p.o.*, respectively.

In accordance with those in vitro antioxidant effects, the hepatoprotective activity of E-DRS in mice was also used here to evaluate its antioxidant capacity in vivo. As SAA is more expensive, we selected vitamin C and resveratrol as positive drugs for economic reasons in this part. The results are shown in Table 1.

There are no significant differences in body weight or food intake among seven experimental groups (data not shown). However, the level of hepatic malondialdehyde (MDA), a well-accepted hallmark of oxidative stress, in $CCl_4$-treated mice increased remarkably, indicating increased lipid peroxidation and oxidative stress in the liver. Oral administration of E-DRS dose-dependently and significantly reduced $CCl_4$-induced oxidative stress as evidenced by reduced MDA contents, increased GSH level, and elevated CAT and SOD-like activities in mice liver (all $p < .05$). It should be noted that E-DRS can protect the liver against $CCl_4$-induced oxidative damage even at a low concentration (10 μmol/kg day, E-$DRS_L$ group) in the present study. In addition, the protective effect of E-DRS at high doses (100 μmol/kg day, E-$DRS_H$ group) is obviously better than that of Vit C (100 μmol/kg day) and RES (100 μmol/kg day) ($p < .05$), suggesting a potent antioxidant effect of E-DRS in vivo.

## 4 | CONCLUSION

In this study, we successfully designed and synthesized a new SAA analog, E-EDRS, which uses RES structure and an amine group to replace the 3′,4′-dihydroxy-*trans*-stilbene group, and the ester structure of SAA, respectively. E-DRS exhibited powerful antioxidant activities both in vitro and in vivo, and its antioxidant activity in vitro was stronger than SAA significantly. The mechanism includes direct scavenging effects on free radical species as well as indirect antioxidant capacities via promoting the activities of the antioxidant enzyme, such as CAT and SOD. The new SAA analog could be used as a new powerful antioxidant resource after further optimization and evaluation.

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### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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