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Antioxidant Properties of Novel Dimers Derived from Natural β-Elemene through Inhibiting H_2O_2-Induced Apoptosis

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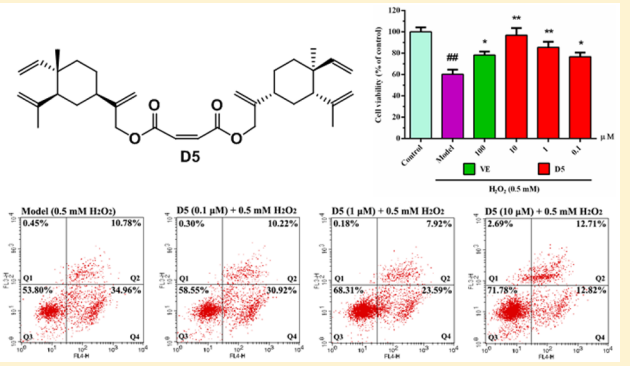
Supporting Information

ABSTRACT: A series of novel β-elemene dimer derivatives were synthesized and evaluated for their antioxidant activities. The results indicated that most of the target compounds showed more potent cytoprotective effects than positive control vitamin E. In particular, dimer **D5** exhibited the strongest antioxidant activity, which was significantly superior to the active compound **D1** obtained in our previous study. Besides, **D5** did not produce obvious cytotoxicity in normal human umbilical vein endothelial cells (HUVECs) and increased the viability of HUVECs injured by H_2O_2 in a concentration-dependent manner. Further studies suggested that the cytoprotective action of **D5** might be mediated, at least in part, by increasing the intracellular superoxide dismutase activity and nitric oxide secretion as well as decreasing the intracellular malonyldialdehyde content and lactate dehydrogenase release. Furthermore, **D5** observably inhibited ROS generation and prevented H_2O_2-induced apoptosis in HUVECs possibly via inhibiting the activation of the MAPK signaling pathway.



KEYWORDS: *β-Elemene, dimer, antioxidant activity, apoptosis, MAPK pathway*

Cardiovascular diseases are the leading cause of death in the world, accounting for nearly 30% of the annual global mortality.[1] Atherosclerosis is the underlying pathological process of many diseases in the cardiovascular system.[2] Although hypercholesterolemia has traditionally been considered as a major cause of atherogenesis, it has now been widely appreciated that endothelial dysfunction is a characteristic feature and key initiating event in the development of atherosclerosis.[3−5] There is evidence that excessive production of reactive oxygen species (ROS) such as OH•, O_2^-, and H_2O_2 is able to evoke vascular endothelial cells (VECs) injury and induce VECs apoptosis, which is frequently linked with endothelial dysfunction.[6−8] VECs apoptosis disrupts the integrity of the endothelial monolayer, which causes degeneration of vascular structures and increase of endothelial permeability, thus exposing the underlying cell layers to a deleterious inflammatory process, contributing to the formation of atherosclerotic lesions.[9,10] Therefore, antioxidants that preferentially inactivate ROS may be an effective strategy for the prevention and treatment of atherosclerosis.

β-Elemene (**1**, Figure 1), a natural sesquiterpene isolated from the essential oils of *Curcuma wenyujin*, has been approved by the Chinese Food and Drug Administration for the treatment of human cancers.[11,12] Because of its low toxicity, β-elemene is well tolerated and accepted by patients with cancers.[13,14] Recent studies have discovered that β-elemene possessed moderate antioxidant effect against oxidative damage. It may protect the endothelial cells from injury induced by H_2O_2 *in vitro* and inhibit neointimal hyperplasia *in vivo* after vascular injury.[15] In addition, it may block H_2O_2-induced monocyte-endothelial cells interactions *in vitro*[16] and retard the progression of atherosclerosis *in vivo*.[17] Our previous studies indicated that β-elemene ester derivatives had more potent antioxidant activities than parent compound β-elemene in H_2O_2-injured human umbilical vein endothelial cells (HUVECs). Especially, the two 13-monosubstituted dimers (**D1**

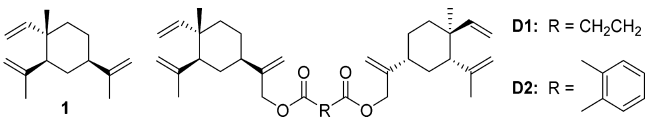


Figure 1. Structures of β-elemene (**1**) and dimers **D1** and **D2**.

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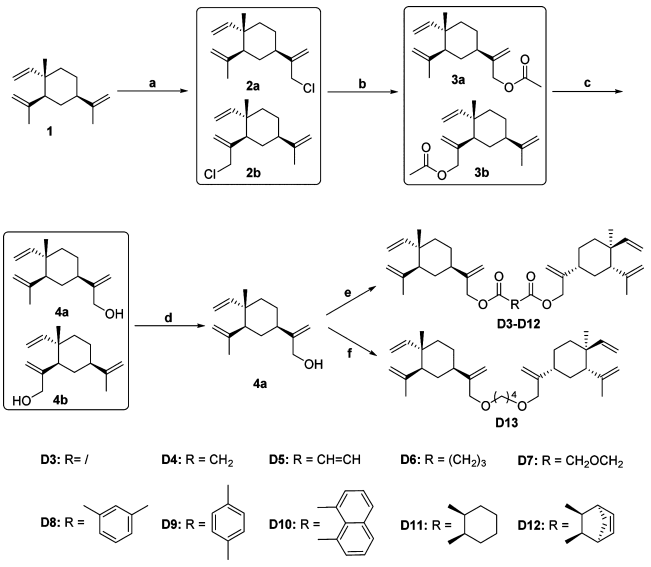
and **D2**, Figure 1) exhibited the most potent antioxidant activities, which were significantly superior to that of positive control vitamin E.[18]

Encouraged by the above findings, in our ongoing studies, we further designed and synthesized a series of novel 13-monosubstituted β-elemene dimer derivatives to improve the antioxidant activity of natural β-elemene. Herein, we report their synthesis, antioxidant activity, and antioxidant mechanism in H_2O_2-treated HUVECs.

The β-elemene dimer derivatives **D3**–**D12** were synthesized according to our previous work.[18] As depicted in Scheme 1, reaction of β-elemene with NaClO afforded the chlorinated mixture of **2a** and **2b**, which was directly reacted with NaOAc to give the acylated compounds **3a** and **3b**. Then the resulting products were subjected to alkaline hydrolysis to produce a mixture of **4a** and **4b**, which was separated by HPLC to provide the main product 13-β-elemol (**4a**). Finally, **4a** reacted with anhydrides/EDCI/DMAP or acyl chlorides/DMAP/Et_3N to yield the target compounds **D3**–**D12**. Dimer **D13** was obtained from alkylation of **4a** with 1,4-dibromobutane in the presence of NaH.

Scheme 1. Synthetic Routes of Dimers D3–D13[a]



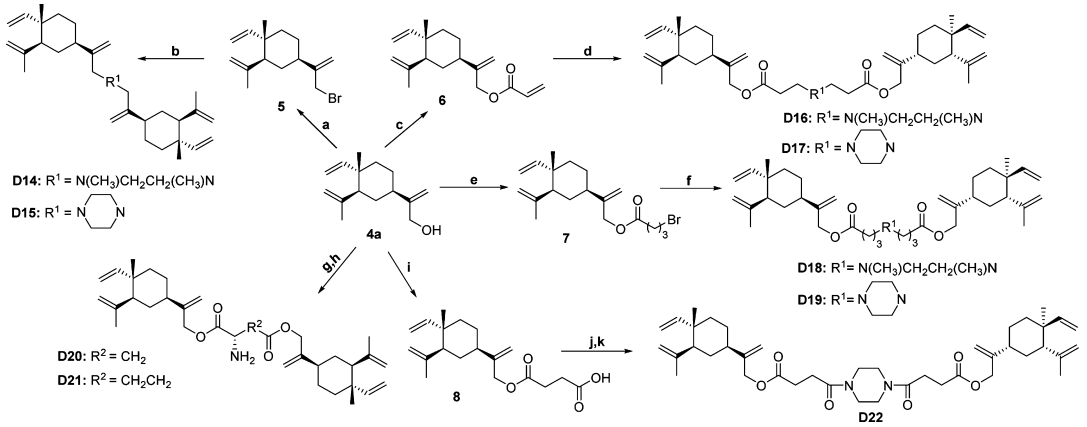
[a]Reagents and conditions: (a) NaClO, HOAc/CH_2Cl_2, 0–5 °C, 6 h, 55%; (b) DMF, NaOAc, 120 °C, 8 h, 75%; (c) MeOH/$CHCl_3$, KOH, reflux, 2 h, 85%; (d) separated by HPLC, hexane/EtOH = 98/2 (V/V), UV = 214 nm; (e) anhydrides/EDCI/DMAP or acyl chlorides/DMAP/Et_3N, CH_2Cl_2, rt, 2–8 h, 74–87%; (f) $Br(CH_2)_4Br$, NaH, anhydrous DMF, rt, 3 h, 47%.

The preparation of dimers **D14**–**D22** was illustrated in Scheme 2. Reaction of **4a** with NBS/PPh_3 gave the brominated intermediate **5**, which was treated with *N*,*N*′-dimethylethylenediamine or piperazine to afford dimer **D14** or **D15**. Treatment of **4a** with 3-bromopropionyl chloride in the presence of DMAP/TEA led to intermediate **6**, followed by treatment with *N*,*N*′-dimethylethylenediamine or piperazine through the Michael addition reaction to provide dimer **D16** or **D17**. Reaction of **4a** with 4-bromobutyric acid in the presence of DCC and DMAP produced intermediate **7**, which was treated with *N*,*N*′-dimethylethylenediamine or piperazine to give dimers **D18** or **D19**. Compound **4a** reacted with Boc-L-Asp-OH or Boc-L-Glu-OH in the presence of EDCI and DMAP, the resulting intermediate followed the *N*-Boc deprotection using TFA to give dimer **D20** or **D21**. Treatment of **4a** with succinic anhydride in the presence of DMAP/TEA gave intermediate **8**, followed by its conversion to the acyl chloride intermediate using oxalyl chloride, which then reacted with piperazine to provide dimer **D22**.

The synthesis of dimer compounds **D23**–**D32** was shown in Scheme 3. Reaction of **4a** with propiolic acid/DCC/DMAP or 3-bromopropyne in the presence of NaH gave intermediate **9** or **10**. Treatment of **4a** with BrR^3COOH/DCC/DMAP provided intermediate **11**, which was further reacted with NaN_3 to afford intermediate **12**. Similarly, intermediate **13** was prepared from reaction of dibromoalkane with NaN_3. Then, treatment of **9** or **10** with **12** or **13** through "click reaction" gave dimers **D23**–**D28** or **D29**–**D32**, respectively.

Based on the structures of dimers **D1** and **D2**, dimers **D3**–**D13** were initially prepared and evaluated for their protective effects on

Scheme 2. Synthetic Routes of Dimers D14–D22[a]



[a]Reagents and conditions: (a) NBS/PPh_3, CH_2Cl_2, rt, 10 min, 88%; (b) *N*,*N*′-dimethylethylenediamine or piperazine, TEA, DMF, 100 °C, 1 h, 73–76%; (c) $Br(CH_2)_2COCl$, DMAP, TEA, rt, 2 h, 78%; (d) *N*,*N*′-dimethylethylenediamine or piperazine, THF/MeOH, 80 °C, 1.5 h, 58–62%; (e) $Br(CH_3)_3COOH$, DCC, DMAP, rt, 6 h, 87%; (f) *N*,*N*′-dimethylethylenediamine or piperazine, TEA, dry DMF, 100 °C, 4 h, 62–67%; (g) Boc-L-Asp-OH or Boc-L-Glu-OH, EDCI, DMAP, CH_2Cl_2, rt, 4 h; (h) TFA, CH_2Cl_2, rt, 2 h, 62–66%; (i) succinic anhydride/DMAP/TEA, CH_2Cl_2, rt, 2 h; (j) oxalyl chloride, cat. DMF, CH_2Cl_2, rt, 1.5 h; (k) piperazine, DMAP, TEA, CH_2Cl_2, rt, 1 h, 55%.

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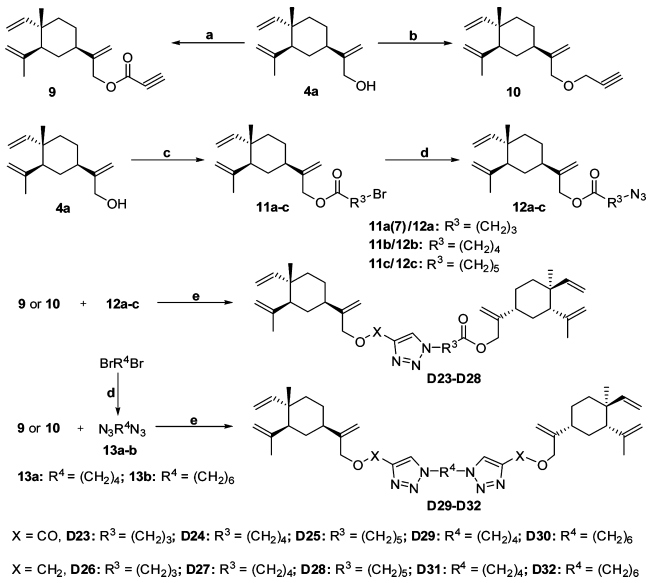
Scheme 3. Synthetic Routes of Dimers D23−D32[a]



X = CO, **D23**: $R^3 = (CH_2)_3$; **D24**: $R^3 = (CH_2)_4$; **D25**: $R^3 = (CH_2)_5$; **D29**: $R^4 = (CH_2)_4$; **D30**: $R^4 = (CH_2)_6$

X = CH_2, **D26**: $R^3 = (CH_2)_3$; **D27**: $R^3 = (CH_2)_4$; **D28**: $R^3 = (CH_2)_5$; **D31**: $R^4 = (CH_2)_4$; **D32**: $R^4 = (CH_2)_6$

[a]Reagents and conditions: (a) propiolic acid, DCC, DMAP, ice-water bath, 6 h, 54%; (b) 3-bromopropyne, NaH, dry DMF, rt, 3 h, 72%; (c) BrR_3COOH, DCC, DMAP, CH_2Cl_2, 6−8 h, 78−85%; (d) NaN_3, DMF, 80 °C, 4 h, 81−87%; (e) AscNa, $CuSO_4{\cdot}5H_2O$, CH_2Cl_2/H_2O, rt, 8−12 h, 62−73%.

H_2O_2-injured HUVECs by MTT assay. **D1**, **D2**, and vitamin E (**VE**) were chosen as positive controls in the experiments. As shown in Figure 2, all of the synthesized compounds showed more potent cytoprotective effects than **VE** in H_2O_2-injured HUVECs. Among them, compound **D5** exhibited the strongest antioxidant activity, which was significantly superior to the active compound **D1**, indicating that introduction of a double bond into in the linker may be beneficial for the activity. It was found that improvement of the activity was acquired by increasing the linear alkyl chain length such as **D3** < **D4** < **D6**. Replacement of CH_2CH_2 in **D1** with CH_2OCH_2 (**D7**) led to decreased activity. When the alkyl chain was substituted by the phenyl ring (e.g., **D8**, **D9**), the activity remarkably decreased. Reducing the phenyl ring to saturated cyclohexane had no effect on the activity (e.g., **D11**, **D12**). It is surprising that the activity was slightly enhanced when the phenyl ring was replaced with the naphthalene ring (**D10**). Changing the ester bond in **D1** to the ether bond (**D13**) resulted in markedly increased activity, suggesting the ester bond maybe not essential for the activity.

It is well-known that the poor solubility of β-elemene limits its application in clinic.[19] To address this issue, dimers **D14−D32** were further prepared through introducing some water-soluble moieties such as amine and triazole. As depicted in Figure 2, most of them showed potent antioxidant activities, which were superior to **VE** or comparable to **D2**. Introduction of amine groups into the alkyl linker (e.g., **D16**, **D17**) showed stronger activity than those linked with β-elemene directly via the amine bond instead of the ester bond (e.g., **D14**, **D15**). Moreover, increasing the linker length of **D16** or **D17** by two carbons (**D18** or **D19**) had no significant effect on the activity. Whereas change of the amine bond in **D19** to the amido bond (**D22**) led to slightly decreased activity. When succinic anhydride in **D1** was substituted by L-Asp-OH (**D20**), the activity remarkably reduced, suggesting that introduction of a polar amino group ($-NH_2$) into the linker has a detrimental effect on the activity. Surprisingly, replacement of L-Asp-OH (**D20**) with L-Glu-OH (**D21**) led to further decreased activity. When the ester bond in **D23−D25** or **D29−D30** was converted to the ether bond (**D26−D28** or **D31−D32**), the activity was less influenced. It was observed that the activity gradually enhanced when the R^3 length was increased from C_3 to C_5 (e.g., **D26** < **D27** < **D28**). Similarly, extending the R^4 length from C_4 to C_6 resulted in slightly improved activity (e.g., **D31** < **D32**). Besides, comparison of the activities of **D23−D28** with **D29−D32** suggested that compounds containing one triazole were obviously preferred. However, the structural modifications by introducing such water-soluble moieties did not result in markedly increased activity. Dimer **D5** showed the strongest antioxidant activity in all the target compounds.

Subsequently, dimer **D5** at lower concentrations was examined for the antioxidant activity in H_2O_2-injured HUVECs. As seen in Figure 3A, **D5** at concentrations of 10, 1, 0.1, and 0.01 μM increased the survival rate of HUVECs by 96.97%, 85.53%, 76.72%, and 65.47% from 60.21% in the model group, respectively. The results indicated that **D5** improved the cell viability in a dose-dependent manner, and the EC_{50} value of **D5** was 0.22 μM. It was proved that **D5** could protect HUVECs from H_2O_2-induced cell injuries.

To exclude the proliferative effect of dimer **D5**, we further checked its cytotoxicity on normal HUVECs by MTT assay. As shown in Figure 3B, the cell viability was above 90% after incubation with **D5** at concentrations of 0.1−50 μM for 24 h. The results indicated treatment with **D5** at these doses did not significantly influence cell proliferation. In addition, the concentrations of the target compound used in this experiment did not lead to more than 50% cell killing, suggesting **D5** had low

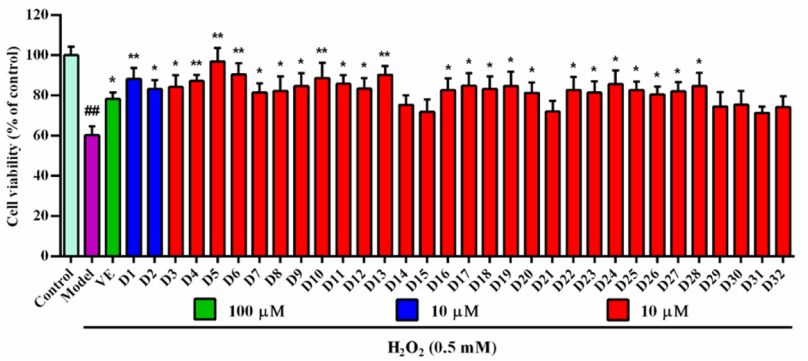


Figure 2. Effects of β-elemene dimer derivatives on the viability of H_2O_2-injured HUVECs. Results are expressed as means ± SD, $n = 3$. $^{\#\#}P < 0.01$ vs control group, $^{*}P < 0.05$, $^{**}P < 0.01$ vs model group.

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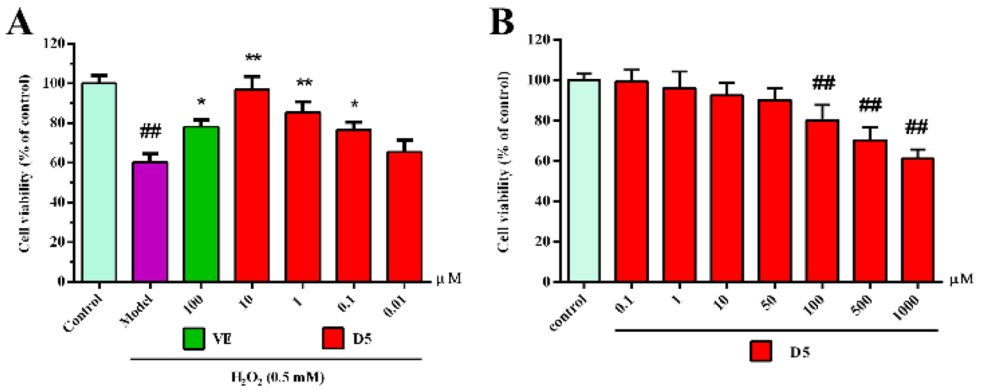

Figure 3. Effects of dimer **D5** on the viability of H_2O_2-injured (A) and normal (B) HUVECs. Results are expressed as means ± SD, $n = 3$. $^{\#\#}P < 0.01$ vs control group, $^{*}P < 0.05$, $^{**}P < 0.01$ vs model group.

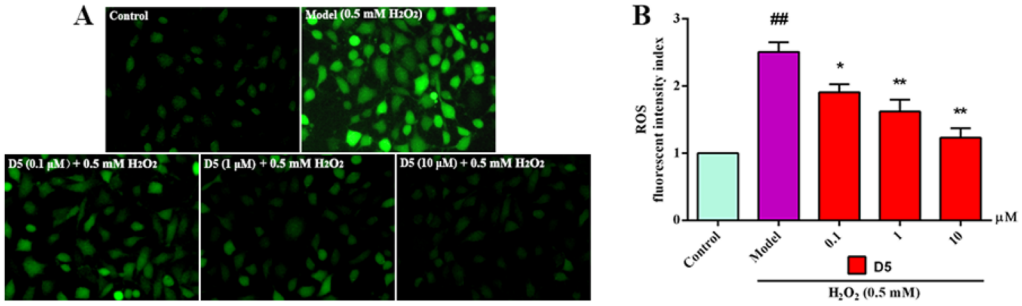

Figure 4. ROS inhibitory activity of dimer **D5** in H_2O_2-injured HUVECs. (A) Shown are representative images of DCF fluorescence in HUVECs with or without treatment. (B) ROS fluorescent intensity index was expressed as the percentage of the control group fluorescence intensity. Results shown are expressed as means ± SD, $n = 3$. $^{\#\#}P < 0.01$ vs control group, $^{*}P < 0.05$, $^{**}P < 0.01$ vs model group.

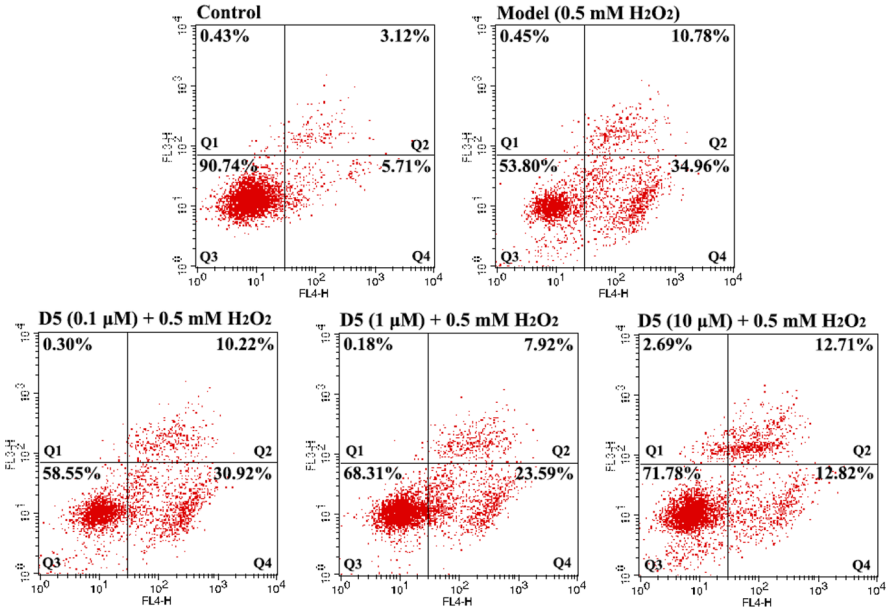

Figure 5. Effect of dimer **D5** on H_2O_2-induced cell apoptosis.

cytotoxicity. As a result, dimer **D5** with concentrations of 10, 1, and 0.1 μM was selected for subsequent mechanism study.

The maladaptive state of impaired HUVECs is characterized by abnormal metabolism of some active substances. The malonyldialdehyde (MDA) content often reflects the extent of lipid peroxidation in an organism and the level of cell damage.[20] Antioxidant enzymes, such as superoxide dismutase (SOD), modulate basal levels of superoxide and protect against endothelial dysfunction, ensuing vasomotor and trophic response.[2] Nitric oxide (NO) is one of the important molecules synthesized by endothelial cells, and NO bioavailability is regarded as the primary marker for endothelial dysfunction.[21] Lactate dehydrogenase (LDH) release into the bloodstream was usually used as an indicator for the integrity of cell membranes or necrosis in response to the oxidant burden.[22] Incubation of HUVECs with 0.5 mM H_2O_2 for 2 h led to notable decrease in the

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intracellular SOD activity and NO secretion, and increase in the intracellular MDA content and LDH release, compared to that of the control group. However, it was observed that the pretreatment with **D5** at concentrations of 0.1, 1, and 10 μM for 24 h significantly increased SOD activity and NO secretion, and decreased MDA content and LDH release in a concentration-dependent manner (see Supporting Information Figure S1). The results suggest that the mechanism underlying the protective action of **D5** may be involved in reducing the changes of these bioactive substances in H_2O_2-injured HUVECs.

Vascular endothelial dysfunction often represents the first step in the development of atherosclerosis.[4] The accumulation of ROS contributes to VEC apoptosis, the leading cause of endothelial dysfunction.[8] Thus, dimer **D5** was examined for its ROS inhibitory activity. As shown in Figure 4, the pretreatment with **D5** at concentrations of 0.1−10 μM decreased the level of ROS from 2.40 to 1.16 as compared to 3.30 in the model group. The results indicated that **D5** could significantly inhibit ROS generation in a dose-dependent manner.

To verify whether the cytoprotective effect of dimer **D5** is associated with inhibition of cell apoptosis, an Annexin V-APC/7-AAD binding assay was performed by flow cytometry. As shown in Figure 5, incubation of HUVECs with 0.5 mM H_2O_2 for 2 h resulted in 45.74% apoptotic cells (Q2 + Q4) as compared with 8.83% in an untreated control group. While the cells were pretreated with **D5** at concentrations of 0.1, 1, and 10 μM for 24 h, the percentage of apoptotic cells decreased to 41.14%, 31.51%, and 25.53%, respectively. The results indicated that **D5** potently inhibited H_2O_2-induced cell apoptosis in a concentration-dependent manner.

It was reported that mitogen activated protein kinases (MAPKs) such as ERK1/2, JNK, and p38 can be regulated by oxidative stress. ROS activates and phosphorylates MAPKs, which modulates cell proliferation, apoptosis, and program.[23,24] ROS-induced apoptosis may be aggravated through the activation of the MAPK pathway. As shown in Figure 6, **D5** markedly

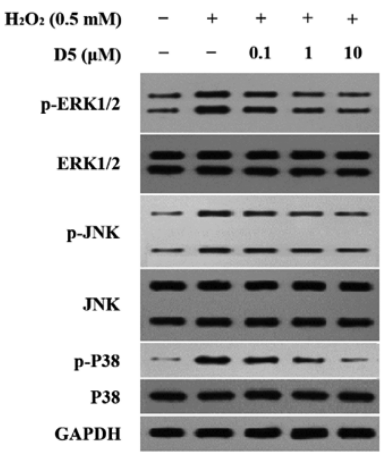

Figure 6. Effect of dimer **D5** on the MAPK phosphorylation in H_2O_2-injured HUVECs.

inhibited the H_2O_2-induced activation of p-ERK1/2, p-JNK, and p-p38 in a concentration-dependent manner, while the total protein expressions of ERK1/2, JNK, and p38 were not altered upon H_2O_2 and/or **D5** treatment. The results suggest that **D5** may prevent H_2O_2-induced apoptosis of HUVECs through inhibiting the activation of MAPK pathway.

In summary, a series of novel β-elemene dimer derivatives were synthesized, and their antioxidant activities were evaluated in H_2O_2-injured HUVECs. The bioassay results indicated that most of the compounds markedly increased the survival rate of HUVECs compared to the model group. Among them, dimer **D5** exhibited the most potent antioxidant activity, which was significantly superior to positive control vitamin E and the active compound **D1**. Besides, **D5** did not produce significant cytotoxicity in normal HUVECs and increased the viability of HUVECs injured by H_2O_2 in a concentration-dependent manner. Further studies demonstrated that the cytoprotective action of **D5** was possibly mediated, at least in part, through affecting the changes of various bioactive substances (e.g., SOD, MDA, NO, LDH) in H_2O_2-treated HUVECs. Furthermore, **D5** markedly inhibited ROS generation and prevented H_2O_2-induced apoptosis of HUVECs potentially by inhibiting the activation of the MAPK signaling pathway. Collectively, the current study may provide a new insight for the treatment of cardiovascular diseases such as atherosclerosis related to oxidative stress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.7b00035.

Synthetic methods and characterization of target compounds; procedures for pharmacological activities (PDF)

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

EDCI, 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DMAP, 4-dimethylamiopryidine; TEA, triethylamine; TFA, trifluoroacetic acid; DMF, *N*,*N*-dimethylformamide; NBS, *N*-bromosuccinimide; PPh_3, triphenylphosphine; THF, tetrahydrofuran; AscNa, sodium ascorbate

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