Tropical Journal of Pharmaceutical Research November 2026; 25 (11): 1503-1508
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
https://dx.doi.org/10.4314/tjpr.v25i11.2

Original Research Article

Protective effects of cryptotanshinone on oxidized low-density lipoprotein-induced endothelial dysfunction in human umbilical vein endothelial cells

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Sent for review: 2 May 2026 *Revised accepted: 12 November 2026*

Abstract

Purpose: *To determine whether cryptotanshinone (CTS) protects against oxidized low-density lipoprotein (oxLDL)-induced endothelial dysfunction in human umbilical vein endothelial cells (HUVECs).*
Methods: *CTS was dissolved in dimethyl sulfoxide (DMSO) to prepare a 200 mM stock solution and diluted to 1, 2.5, 5, 10, and 20 µM working concentrations. HUVECs were challenged with oxLDL (100 µg/mL) and co-treated with CTS for 24 h; activated simvastatin (0.1 µM) served as a positive control. Endothelial permeability was measured by fluorescein isothiocyanate (FITC)-dextran transwell flux, and nitric oxide (NO) bioavailability was quantified as total nitrate/nitrite using a fluorometric assay.*
Results: *OxLDL significantly increased endothelial permeability compared with untreated cells ($p < 0.005$). CTS at 1, 2.5, and 5 µM reduced oxLDL-induced hyperpermeability ($p < 0.005$), and 10 µM remained protective ($p < 0.01$); 20 µM was not significantly protective ($p > 0.05$). OxLDL also reduced NO bioavailability ($p < 0.005$). CTS restored NO at 2.5 µM ($p < 0.05$), 5 µM ($p < 0.01$), and 10 and 20 µM ($p < 0.005$), whereas 1 µM was not significant ($p > 0.05$).*
Conclusion: *CTS attenuated two functional manifestations of oxLDL-induced endothelial dysfunction in vitro: loss of endothelial barrier integrity and reduced nitric oxide bioavailability. These findings provide functional evidence supporting further mechanistic, dose-optimization, and translational evaluation of CTS as an endothelial-protective compound in early atherogenic injury.*

Keywords: *Cardiovascular disease, Cryptotanshinone, Endothelial dysfunction, HUVECs, Nitric oxide, Oxidized low-density lipoprotein, Vascular protection*

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INTRODUCTION

Cardiovascular diseases remain a major cause of mortality worldwide, and atherosclerosis underlies many ischemic cardiovascular events. Endothelial dysfunction is an early and biologically important stage of this disease because the endothelium regulates vascular tone, selective permeability, inflammatory-cell trafficking, and thrombosis [1-4]. Atherogenesis

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refers to the multistep development of an atherosclerotic lesion, beginning with endothelial dysfunction and retention or modification of lipoproteins in the arterial wall, followed by leukocyte recruitment, foam-cell formation, and progressive plaque growth. Loss of endothelial homeostasis therefore creates a permeable, inflammatory, and pro-thrombotic vascular surface that favors lesion initiation and progression [2-5]. Oxidized low-density lipoprotein (oxLDL) is a major mediator of early atherogenic injury. It promotes endothelial activation, oxidative stress, inflammatory signaling, and barrier disruption while reducing nitric oxide (NO) bioavailability and perturbing endothelial nitric oxide synthase signaling [4-7]. Together, these abnormalities favor leukocyte recruitment, lipid entry and retention within the sub-endothelial space, and persistence of vascular inflammation, thereby accelerating lesion formation [5-7]. Natural products remain an important source of compounds with potential vascular-protective activity [8-10]. *Salvia miltiorrhiza* Bunge (Danshen) is a perennial medicinal species of the family Lamiaceae whose dried root is used extensively in traditional Chinese medicine. The species is cultivated widely across China; it is native mainly to North-central, South-central, and Southeastern China, and extends into Vietnam [11,12]. Its major lipophilic constituents are tanshinones, a group of abietane-type diterpenoid quinones that includes cryptotanshinone (CTS), tanshinone I, tanshinone IIA, and dihydrotanshinone [11]. These compounds, particularly CTS, have demonstrated anti-inflammatory, antioxidant, and vasoregulatory activities, while recent reviews indicate that CTS can modulate redox signaling, inflammatory cascades, apoptosis, and endothelial-injury pathways [13,14].

Previous *in vitro* work showed that CTS can attenuate endothelial injury triggered by tumor necrosis factor-alpha (TNF-alpha) and oxLDL [15,16]. The present study focused on oxLDL because it directly reproduces a key pro-atherogenic insult associated with endothelial barrier failure and loss of NO signaling. Human umbilical vein endothelial cells (HUVECs) were selected as a primary human endothelial model because they form reproducible confluent monolayers, retain characteristic endothelial functions, and are widely used to investigate vascular permeability and NO responses. Importantly, the same cell model has been used in earlier CTS and oxLDL studies, enabling direct comparison with the existing evidence [17-19]. Accordingly, this study evaluated whether CTS modifies endothelial permeability and NO bioavailability in oxLDL-stimulated HUVECs.

EXPERIMENTAL

Materials

Human umbilical vein endothelial cells were obtained from Cascade Biologics (Portland, Oregon, USA) as cryopreserved primary cultures and maintained in M200 growth medium supplemented with 2 % low-serum growth supplement according to the manufacturer's instructions. Cryptotanshinone was purchased from ChromaDex (USA) and dissolved in dimethyl sulfoxide (DMSO; Calbiochem, UK) to prepare a 200 mM stock solution. Oxidized low-density lipoprotein was purchased from Kalen Biomedical (USA). Simvastatin (purity ≥ 98 %) was obtained from Bender MedSystems (Vienna, Austria) and used as the positive-control compound [19]. The *In Vitro* Vascular Permeability Assay Kit was obtained from Millipore (USA), and the Nitrate/Nitrite Fluorometric Assay Kit was purchased from Cayman Chemical (USA).

Preparation of simvastatin solution

Before cell treatment, the lactone form of simvastatin was converted to its active hydroxy acid form using a published *in vitro* activation procedure [20]. Simvastatin (4 mg) was dissolved in 100 µL absolute ethanol, followed by addition of 150 µL 0.1 N sodium hydroxide. The mixture was maintained at 50 °C for 2 h to hydrolyze the lactone ring, neutralized to pH 7.2 with 0.1 N hydrochloric acid, and brought to a final volume of 1 mL with deionized water [20].

Assessment of endothelial permeability

Endothelial permeability was assessed with the *In Vitro* Vascular Permeability Assay Kit using a collagen-coated transwell model, following the manufacturer's protocol with modifications consistent with published endothelial barrier assays [19,21]. HUVECs were seeded on the inserts and cultured to a confluent monolayer. The experimental controls comprised a cell-free insert (NC; no-cell permeability control), untreated confluent HUVECs (N; normal control), oxLDL-treated HUVECs without CTS (C; injury control), and simvastatin-treated cells (positive control). Hyperpermeability was induced with oxLDL (100 µg/mL) for 24 h, and CTS (1, 2.5, 5, 10, or 20 µM) was added concurrently for the same 24 h period. Simvastatin (0.1 µM) served as the positive control. After treatment, fluorescein isothiocyanate-dextran (FITC-dextran, 4 kDa; 1:50 dilution) was added to the apical chamber for 5 min, a duration used in established HUVEC permeability procedures.

Basal-chamber fluorescence was then measured and expressed as permeability index (%) [15,16].

Determination of nitric oxide (NO) bioavailability

Nitric oxide bioavailability was estimated from total nitrate/nitrite in culture supernatants using the Nitrate/Nitrite Fluorometric Assay Kit (Cayman Chemical), an approach based on fluorometric detection of stable NO oxidation products. HUVECs were cultured in 24-well plates until confluent. Untreated cells served as the normal control (N), whereas cells exposed to oxLDL (100 µg/mL) without CTS served as the injury control (C). CTS at 1, 2.5, 5, 10, or 20 µM was added concurrently with oxLDL for 24 h; simvastatin (0.1 µM) served as the positive control. After 24 h, culture media were collected and nitrate/nitrite was measured according to the kit protocol. Fluorescence was read with a Tecan Infinite M200 microplate reader (Männedorf, Switzerland) at 365 nm excitation and 430 nm emission [16,22].

Statistical analysis

Data were presented as mean ± standard error of the mean (SEM) from three independent experiments. Group differences were evaluated by one-way analysis of variance, followed by Dunnett's or Tukey's multiple-comparison test, as appropriate. Statistical significance was determined at $p < 0.05$.

RESULTS

Effect of CTS on endothelial permeability

OxLDL (100 µg/mL) produced a significant increase in permeability relative to untreated HUVEC monolayers ($p < 0.005$; Figure 1). Co-treatment with CTS significantly attenuated the oxLDL-induced increase at 1, 2.5, and 5 µM (all $p < 0.005$ versus the oxLDL control), with the greatest protection at 5 µM. CTS at 10 µM also reduced permeability ($p < 0.01$), whereas 20 µM did not differ significantly from the oxLDL control ($p > 0.05$). Simvastatin significantly reduced hyperpermeability ($p < 0.005$). Thus, CTS preserved endothelial barrier function across the low-to-moderate concentration range but not at the highest concentration tested.

Cells were co-treated with CTS and oxLDL (100 µg/mL) for 24 h before FITC-dextran permeability measurement. Data were expressed as mean ± SEM (n = 3). ***$p < 0.005$ and **$p < 0.01$ versus the oxLDL-treated control (C). NC, no-cell permeability control; N, normal untreated HUVEC control; C, oxLDL-treated HUVEC control; CTS, cryptotanshinone; Sim, simvastatin.

Effect of CTS on nitric oxide bioavailability

OxLDL significantly reduced NO bioavailability relative to normal untreated HUVECs ($p < 0.005$; Figure 2). CTS at 1 µM did not significantly restore NO ($p > 0.05$), whereas 2.5 µM increased NO relative to the oxLDL control ($p < 0.05$), 5 µM produced a larger increase ($p < 0.01$), and 10 and 20 µM produced the strongest responses (both $p < 0.005$). Simvastatin also significantly increased NO bioavailability ($p < 0.05$). These findings indicate that CTS counteracted oxLDL-associated impairment of endothelial NO availability from 2.5 to 20 µM.

Cells were co-treated with CTS and oxLDL (100 µg/mL) for 24 h, and nitric oxide bioavailability was assessed from nitrate/nitrite by fluorometry. Data were expressed as mean ± SEM (n = 3). ***$p < 0.005$, **$p < 0.01$, and *$p < 0.05$ versus the oxLDL-treated control (C). N, normal untreated HUVEC control; C, oxLDL-treated HUVEC control; CTS, cryptotanshinone; Sim, simvastatin.

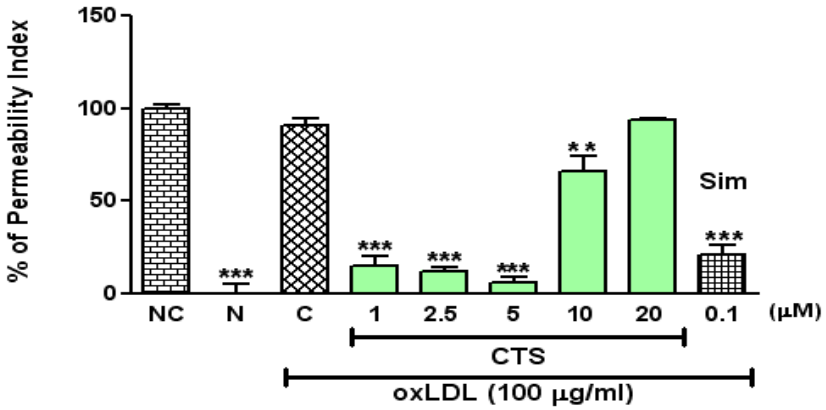

Figure 1: Effect of various concentrations of cryptotanshinone on endothelial permeability in HUVECs

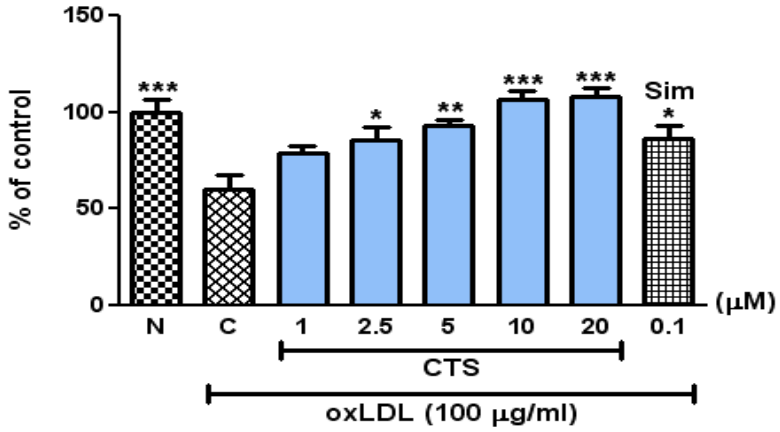

Figure 2: Effect of various concentrations of cryptotanshinone on nitric oxide production in HUVECs

DISCUSSION

This study determined whether cryptotanshinone could mitigate oxLDL-induced endothelial dysfunction in HUVECs using two complementary functional endpoints: endothelial permeability and nitric oxide bioavailability. CTS limited oxLDL-associated barrier disruption and restored NO production within defined concentration ranges. These findings are biologically relevant because increased endothelial permeability and diminished NO availability are established features of early endothelial dysfunction during atherogenesis [1-4]. The permeability data showed that CTS can preserve endothelial barrier function during pro-atherogenic stress. A compromised endothelial barrier facilitates entry of atherogenic lipoproteins and inflammatory mediators into the vessel wall, thereby promoting lipid retention, inflammatory-cell recruitment, and plaque initiation [4,6]. In the present experiments, 5 μM CTS produced the greatest barrier protection. This is consistent with earlier reports that CTS suppresses oxLDL and tumor necrosis factor-alpha-driven endothelial injury [15,16]. Transwell-based FITC-dextran assays have also been used widely to quantify endothelial and epithelial monolayer permeability [19,21].

The non-linear concentration-response pattern deserves attention. Barrier protection was evident at low-to-moderate CTS concentrations, whereas 20 μM did not significantly reduce oxLDL-induced hyperpermeability. This finding may reflect concentration-dependent loss of protective efficacy, off-target activity, or reduced cellular tolerance at the highest exposure. Because cell viability was not measured concurrently in the present experiments, the underlying explanation cannot be established from these data. Current pharmacological evidence similarly indicates that CTS responses may vary according to concentration and experimental context [13,14].

Another major observation was the restoration of NO bioavailability by CTS in oxLDL-treated HUVECs. Physiological NO supports vasodilation, limits leukocyte adhesion and platelet activation, and contributes to vascular homeostasis. Impaired endothelial nitric oxide synthase (eNOS) activity and reduced NO availability are therefore central links between oxidative stress and atherosclerotic vascular injury [4,5]. The increase in nitrate/nitrite measured in this model is consistent with functional recovery of an important endothelial signaling pathway after oxLDL challenge. These results are also consistent with the broader pharmacological literature on *S. miltiorrhiza* and CTS. Evidence indicates that CTS can influence multiple cardiovascular-relevant processes, including oxidative stress, inflammatory signaling, apoptosis, pyroptosis, and endothelial injury responses [13,14].

Earlier work further demonstrated that CTS suppresses endothelin-1 expression while increasing NO production in human vascular endothelial cells [23], providing biological support for the functional effects observed here. The larger nitrate/nitrite response observed at higher CTS concentrations should, however, not be interpreted automatically as a uniformly greater benefit. Restoration of deficient NO signaling is generally vasoprotective, whereas excessive or dysregulated reactive nitrogen chemistry can become harmful in an oxidant-rich environment. Because the present assay quantified nitrate/nitrite accumulation rather than eNOS activity, superoxide production, or peroxynitrite formation, the mechanism responsible for the higher signal at 10 - 20 μM CTS remains uncertain. Future experiments should therefore combine NO measurement with eNOS

phosphorylation, reactive oxygen species (ROS), and nitrosative-stress markers [24,25].

Several limitations qualify the interpretation of these findings. First, an *in vitro* HUVEC model cannot reproduce the full vascular environment, including shear stress, immune-cell interactions, extracellular-matrix remodeling, and systemic metabolic influences [17,18]. Second, the study measured functional endpoints without directly examining upstream mechanisms such as lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), eNOS, tight-junction proteins, adhesion molecules, inflammatory cytokines (such as interferon-g), or ROS [5,7,24,26]. Third, cell viability was not assessed in parallel with permeability and NO, limiting interpretation of the absent barrier protection at 20 μM CTS. Integrating functional assays with molecular readouts and viability assessment would therefore strengthen mechanistic inference [2,7,18].

Future investigations should extend these observations through integrated mechanistic and translational experiments. Priority targets include lectin-like oxidized low-density lipoprotein receptor-1 signaling, eNOS activity, oxidative stress, endothelial-junction proteins, and inflammatory mediators (e.g., interferon-g) during oxLDL exposure [15,16,21, 26]. Parallel viability assays would help define the concentration range in which functional protection occurs without cellular toxicity. *In vivo* validation and pharmacokinetic studies will ultimately be required before CTS can be considered for therapeutic translation in atherosclerosis-related endothelial injury.

CONCLUSION

Cryptotanshinone (CTS) reduces oxidized low-density lipoprotein-induced endothelial hyperpermeability and restores nitric oxide bioavailability in human umbilical vein endothelial cells *in vitro*. The results support a functional endothelial-protective action of CTS under oxLDL challenge, while remaining preliminary because molecular mechanisms, viability at the highest concentration, pharmacokinetics, and *in vivo* efficacy were not assessed. These findings justify targeted mechanistic studies and subsequent *in vivo* validation rather than direct therapeutic inference.

DECLARATIONS

Acknowledgement/Funding

Special thanks to Universiti Putra Malaysia and INTI International University Malaysia for the institutional, research-facility, and administrative support provided for this work. This research was funded by the Research University Grant Scheme, Universiti Putra Malaysia (Project no. 04/01/07/0139RU).

Ethical statement

This *in vitro* study used commercially obtained human umbilical vein endothelial cells and did not directly recruit human participants or use experimental animals; therefore, separate participant informed consent and animal ethical approval were not applicable.

Conflict of interest

The authors declare that there is no conflict of interest associated with this work.

Authors' contributions

All authors contributed to the conception and design of the study, analysis or interpretation of the data, drafting or critical revision of the manuscript, and approval of the final version. All authors agree to be accountable for the integrity of the work.

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