

Vasorelaxant Effects of *Coriandrum sativum* L. Extract on Rat Isolated Aorta

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Received: 21 September, 2020; Accepted: 28 October, 2020; Published: 19 November, 2020

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Abstract

Aim: Coriander (*Coriandrum sativum* L.) is an annual plant belonging to the family Umbelliferae, which distributed in Central and Western Europe, India, Bangladesh, Thailand, China, and other Asian regions. Besides being edible, coriander is an important traditional medicine in India and China, and is used to treat circulatory disorders, such as respiratory, urinary tract, and skin diseases. In this study, we investigated the vasorelaxant effects of extracts from coriander and further studied to clarify their action mechanisms.

Method: The aerial part of coriander, which analyzed the rutin content as its quality evaluation using a chromatographic method (HPLC), was cut and extracted with ethyl acetate or hot water. The extracts were concentrated under the reduced pressure. Vasorelaxant effects of these extracts were assessed on rat isolated aorta. The aorta was placed in a well-oxygenated bath of modified Krebs-Henseleit solution and the mechanical tension was measured isometrically.

Results: These extracts showed vasorelaxant effects on aorta precontracted with 3×10^{-7} M norepinephrine (NE). The ethyl acetate extract showed biphasic vasorelaxation (fast and slowly developing relaxations) on isolated rat aortic rings with endothelium. Fast relaxation disappeared in endothelialized or pre-administration of 10^{-4} M L-NAME monomethylarginine. Furthermore, the hot water extract showed only slowly developing relaxations independent in endothelium. After treatment with the hot water extract, NE-induced phasic vasoconstriction was not inhibited. While the hot water extract inhibited vasoconstrictions induced by a high concentration (60 mM) of K^+ and also showed inhibitory effect on NE-induced vasoconstriction in the presence of nicardipine.

Conclusion: These results suggest that the vasorelaxant effect of ethyl acetate extract of coriander on NE-induced vasoconstriction may be attributed to Nitric Oxide (NO) releasing dependent on endothelium. And the hot water extract of coriander showed vasorelaxant activities attributed to blocking of Ca^{2+} influx via voltage-dependent Ca^{2+} channels (VDCs) and receptor-operated Ca^{2+} channels (ROCs), but not competing for the adrenergic receptor.

Keywords: *Coriandrum sativum*; quality evaluation; vasorelaxant effects; aorta; endothelium; Ca^{2+} channel

Introduction

Coriander (*Coriandrum sativum* L.) is an annual plant belonging to the family Umbelliferae, which originated in the Mediterranean region and distributed wide across Asian regions such as India, Bangladesh, Thailand and China, and central and western Europe such as Italy and the Netherlands [1, 2].

The leaves and seeds of coriander are used for spices in food as well as a medical herb. Especially, in India, it is used as an important crude drug in its traditional medicine, Ayurveda. In Ayurveda, coriander seeds or fruits are used to treat dyspepsia, respiratory and urinary disorders. As a traditional medicine in China, whole plants or seeds are used to improve the indigestion of food [3, 4].

Among the chemical constituents, many monoterpenes such as linalool, α -pinene, and γ -terpene in the essential oil, and phenylpropanoids such as cis-dehydrocarvone have been isolated

from the seed or leaf coriander. Also, it contains long-chain alcohols such as geraniol and tetradodecanol and aldehydes such as decanal. In addition to this, fatty acids such as petroselinic acid, linolenic acid, and oleic acid are contained [2, 5, 6].

Although there are few reports on water-soluble components, the above-mentioned monoterpene glycosides, aromatic compound glycosides, nucleic acid components, and some flavonoid glycosides have been reported [6, 7, 8].

Many bioactivities of coriander were reported. The aqueous extract of coriander seed possesses diuretic activity, the extracts of seed and root possess antioxidative properties [9, 10, 11]. Oral administration of coriander extract in obese-hyperglycemic-hyperlipidemic rats normalized glycemia and decreased the elevated levels of insulin, total cholesterol, LDL-cholesterol, and triglycerides [12]. The aqueous extract from the leaves and stems exhibited a competitive inhibition of α -glucosidase [13]. The

hydro-alcoholic extract of aerial parts prolonged sleep duration in mice [14]. The leaf extract potentiated GABAergic neurons in the mouse brain [15]. The essential oil of coriander exhibited an effective antimicrobial activity against various pathogenic bacteria except for *Bacillus cereus* and *Enterococcus faecalis* [16]. Oral administration of seed extract of coriander could ameliorate aging-induced memory declines in the SAMP8 mice [17]. The leaf extract decreased heavy metals concentrations in the mouse kidney [18].

Regarding the antihypertensive effect, it was reported that the seed extract had cardio depressant actions, a vasodilator effect, a diuretic effect [19], and the leaf extract inhibited angiotensin-converting enzyme [20].

In this study, we focused on the vasorelaxant effects of coriander (especially in its leaf and stem) and investigated the mechanisms in detail.

Materials and Methods

Plant Material

Coriander (*C. sativum*) was harvested and collected at Work Center Tochinoki Farm (Fukuoka, Japan) in January 2020 (Donated from Kinkoh-Seika Co., Ltd., Yokohama, Japan).

Chemicals

Norepinephrine hydrochloride (NE), nicardipine, ethylene glycol-bis(2-aminoethylether)-N,N,N',N'-tetraacetic acid (EGTA), L-N^G-monomethylarginine (LNMMA), and acetylcholine chloride (ACh) were purchased from Sigma Chemical Co. (St. Louis, USA). Rutin trihydrate was purchased from Kanto Chemical Co. Ltd. (Tokyo, Japan).

Quality Evaluation of Coriander

Loss on drying: Aerial part of the coriander was cut to about 10 mm length, and 2-3 g portions were collected, weighed accurately, and then dried (105°C). After 5 hours, the dry portion was weighed and the loss of mass was calculated as the percentage of loss on drying (%) (according to Japanese Pharmacopeia 17th ed. [21]).

Quantity analysis (rutin): Aerial part of coriander was cut using a pulverizing mill, and 3 g portions were collected, weighed accurately, and then boiled with 40% ethanol 100 mL under reflux for 2 hours. The resulting extract was filtrated and added 40% ethanol to make exactly 100 mL (sample solution). Separately, weighed accurately about 10 mg of rutin (purchase from Kanto Chemicals Co. Ltd, as reagent grade), dissolved in 100 µL DMSO and added 40 % ethanol to make exactly 100 mL (standard solution).

The sample solution and standard solution were subject to HPLC analysis (column: YMC Triart C18 4.6×150 mm i.d. (YMC Co., Ltd., Kyoto, Japan). solvent: 14% acetonitrile, detect: 350 nm UV, temperature: 40°C, flow rate: 1 mL/min).

Extraction of Coriander

extracted with 500 mL of ethyl acetate or hot water in reflux. The ethyl acetate extract was evaporated in vacuo to obtain the dried extracts (Coriander ethyl acetate extract (CEAx), 0.30 g, 2.7% (w/w) as dried coriander). The hot water extract was freeze-dried (Coriander hot water extract (CHWx), 2.93 g, 22.8% (w/w) as dried coriander)).

Isolation of Rat Aortic Strips

All animal study protocols were approved by the Ethics Committee at Yokohama University of Pharmacy (Kanagawa, Japan). All experiments using animals were performed in accordance with the Guiding Principles for the Care and Use of Laboratory Animals as approved by the Japanese Pharmacological Society.

Eight-week-old Wistar male rats were purchased from Japan SLC Inc. (Hamamatsu, Japan), and were housed (< 6 rats per cage) in a room maintained at 24 ± 1, humidity 55 ± 5% with a 12 hours light/dark cycle (lights on from 07:00 to 19:00). Food (MR stock MF, Oriental Yeast Co. Tokyo, Japan) and water were available ad libitum.

Experiments were performed according to the method as described in our previous studies [22,23]. In brief, after 7–10 days of habituation, rats weighing 222–286 g were killed by exsanguination from the carotid arteries under anesthesia with isoflurane absorption. A section of the thoracic aorta between the aortic arch and diaphragm was removed and placed in oxygenated, modified Krebs-Henseleit buffer (KHB: NaCl 118.0 mM, KCl 4.7 mM, NaHCO₃ 25.0 mM, CaCl₂ 1.8 mM, NaH₂PO₄ 1.2 mM, MgSO₄ 1.2 mM, and glucose 11.0 mM). The aorta was cleaned and cut in ring preparations 3 mm in length. To detach the endothelium, endothelial cells on each strip were removed by gentle rubbing of the endothelial surface with a disposable cotton applicator.

The tissue was placed in a well-oxygenated (95% O₂, 5% CO₂) bath of KHB 10 mL at 37°C with the ringed aorta connected to a tissue holder and to a force-displacement transducer (TB- 611T; Nihon Kohden, Tokyo, Japan). The tissue was equilibrated for 1 hour under a resting tension of 1.0 g. During this time, the KHB solution in the tissue bath was replaced every 20 minutes at 37°C.

Experimental Protocol

1. After equilibration, each aortic ring was contracted by treatment with 3×10⁻⁷ M NE. The presence of functional endothelial cells was confirmed by demonstrating relaxation with response to 10⁻⁵ M ACh, tissue indicating 80% relaxation of the aortic ring was regarded as tissue with endothelium. The endothelial cells removed by rubbing were confirmed by observing the loss of ACh-induced relaxation (<5%).
2. When the NE (3×10⁻⁷ M) -induced contraction reached its plateau, each sample was added.
3. Some reagent was pre-treatment and adding the NE (3×10⁻⁷ M), after the vasoconstriction reached plateau, each sample was added.
4. For examination of NE-induced contractions in the presence

of sample, aortic rings were exposed to CHWx (3 mg/mL) for 1 hour, and then NE (10^{-5} to 10^{-3} M) was added cumulatively to the aforementioned bath.

5. For examination of Ca^{2+} -induced contraction in depolarized muscle, the aortic rings were exposed to Ca^{2+} -free KHS containing EGTA 0.01 mM and were depolarized with isotonic K^+ (60 mM). The aortic rings were exposed to CHWx (3 mg/mL) for 1 hour, after which Ca^{2+} (10^{-5} to 10^{-3} M) were cumulatively applied to the depolarized aorta in Ca^{2+} -free KHS.

6. For examination of Ca^{2+} -induced contractions in the presence of NE, the aortic rings were exposed to CHWx (0.1 or 0.3 mg/mL) in Ca^{2+} -free KHS containing EGTA 0.01 mM for 1 hour, followed by the addition of nicardipine 10^{-6} M and NE 10^{-6} M. Next, Ca^{2+} (10^{-5} to 10^{-3} M) were added cumulatively to the bath.

7. In each protocol, each extract was dissolved in DMSO and diluted with saline. The final concentration of DMSO in the organ bath was less than 0.1%, which concentration did not affect contraction or relaxation (unpublished data). Unless other specified, all other drugs were dissolved in saline.

Statistical Analysis

The results are expressed as mean $\pm$ SE. Statistical evaluation of data was performed using Tukey's test or Student's t-test for unpaired observations. Values of $P < 0.05$ were considered to indicate significant differences. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [24].

Results

1. Quality evaluation of Coriander: The value of loss on drying (87.6%) and rutin content (0.025% (w/w) as dried coriander) were obtained.

2. Effects of CEAx and CHWx (post-administration) on vasorelaxants of rat aorta:

(1) Effects of CEAx and CHWx on NE-induced vasoconstrictions (post-administration)

CEAx (1 mg/mL) showed biphasic vasorelaxations (fast and slowly developing relaxations). The fast relaxation developing within a few seconds to tens of seconds was observed on the aorta with intact endothelium. This relaxation effect disappeared and only slowly developing relaxations remained in endothelium-

rubbed tissue (Figure 1 A), and pre-treatment with LNMMA at 10^{-4} M inhibited the fast relaxation significant (Figure 2). The fast relaxation effects of CEAx were observed in a concentration-dependent manner at 0.1 to 1.0 mg/mL (Figure 3).

On the other hand, CHWx showed only a slow and sustained relaxations effect developing during several tens minutes (Figure 1 B), and also this effect was observed for aortic rings without endothelium (data not shown). This vasorelaxant effect was observed in a concentration-dependent manner at 0.3 to 3 mg/mL (Figure 4).

(2) Effects of CHWx on NE-induced contraction (pre-administration)

Sixty minutes after treatment with CHWx, aortic rings were

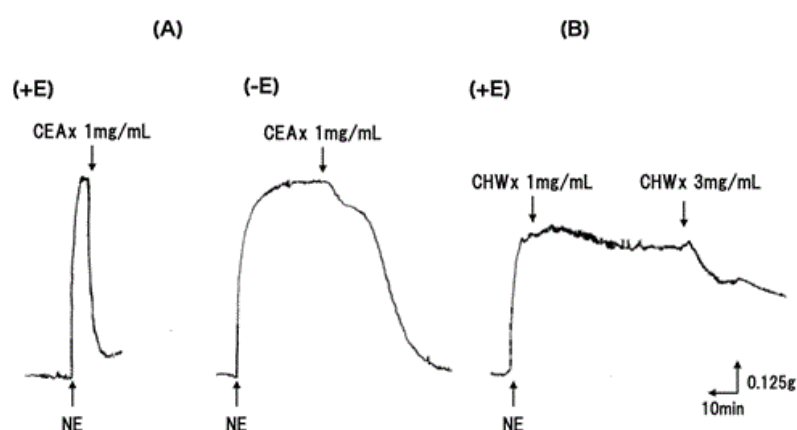


Figure 1: Typical effect of coriander extract on NE-precontracted rat aortic rings

(A) Effect of Coriander ethyl acetate extract (CEAx) on NE-precontracted rat aortic rings with (+E) or without (-E) endothelium
NE: 3×10^{-7} M, CEAx: 1 mg/mL

(B) Effect of Coriander hot water extract (CHWx) on NE-precontracted rat aortic rings with (+E) or without (-E) endothelium
NE: 3×10^{-7} M, CHWx: 1 mg/mL, 3 mg/mL

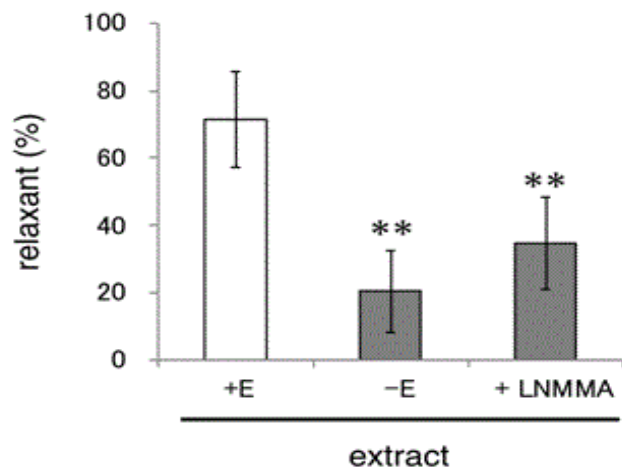


Figure 2: Relaxation responses induced by CEAx in aortic rings precontracted with 3×10^{-7} M NE extract: CEAx: 1mg/mL, +E: with endothelium, -E: without endothelium, +LNMA: 10^{-4} M. Values represent mean $\pm$ SE of 4 determinations. **P < 0.01 vs extract with endothelium (+E)

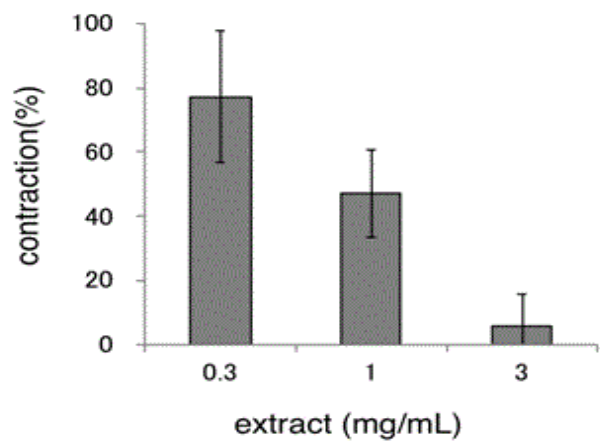


Figure 3: Endothelium-dependent relaxant effect of CEAx in aortic rings precontracted with 3×10^{-7} M NE extract: CEAx: 0.1 to 1mg/mL, Values represent mean $\pm$ SE of 4 determinations

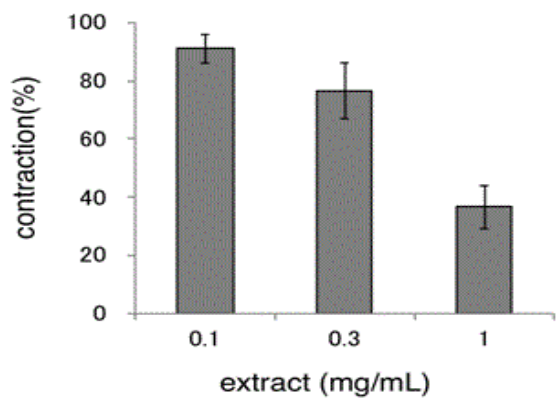


Figure 4: Relaxant effect of CHWx in aortic rings precontracted with 3×10^{-7} M NE extract: CHWx: 0.3 to 3 mg/mL, Values represent mean $\pm$ SE of 4 determinations

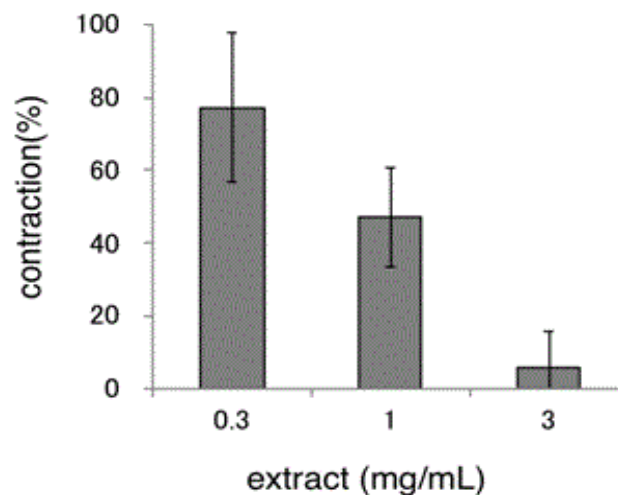


Figure 5: Concentration-response relationships for contractile responses of aortic rings to NE preincubated with CHWx Symbols: - control, -- CHWx 3mg/mL. Values represent mean $\pm$ SE of 4 determinations

contracted by the cumulative addition of NE (10^{-5} to 10^{-3} M) (Figure 5). NE-induced contractions did not affect by treatment with CHWx.

(3) Effects of CHWx on Ca^{2+} -induced contraction of high potassium (60 mM)-stimulated vessels

Ca^{2+} can contract aortic rings in a concentration-dependent manner in Ca^{2+} -free KHB after depolarization with isotonic high potassium (60 mM) by influx via voltage-dependent Ca^{2+} channels (VDCs). CHWx significantly inhibited these contractions (Figure 6).

(4) Effects of CHWx on Ca^{2+} -induced contraction of NE (10^{-6} M)-stimulated aorta in the presence of nicardipine

In addition, the NE (10^{-6} M)-induced contractions of aortic rings in the presence of nicardipine (10^{-6} M) in Ca^{2+} -free KHS occurred in a Ca^{2+} (10^{-5} M to 10^{-3} M) concentration-dependent manner, presumably due to Ca^{2+} influx through ROCs. CHWx inhibit these contractions (Figure 7).

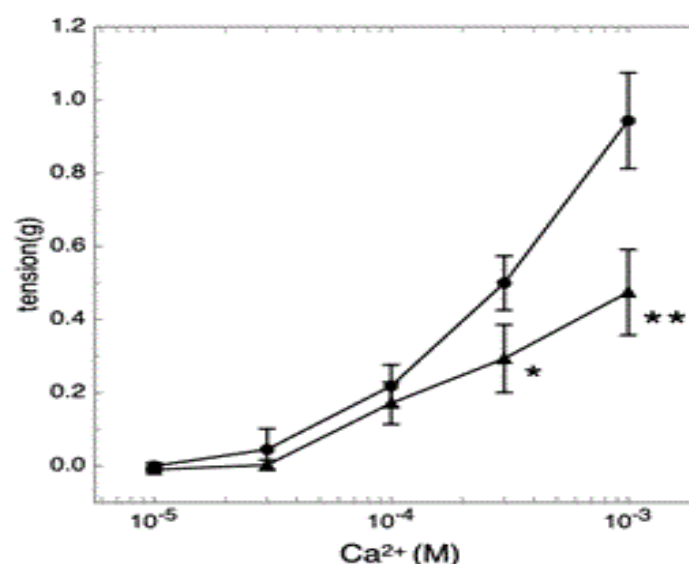


Figure 6: Concentration-response relationships for contractile responses of aortic rings to Ca^{2+} in a Ca^{2+} -free medium preincubated with high potassium (60 mM) Symbols:-- control, -- CHWx 3mg/mL. Values represent mean $\pm$ SE of 4 determinations. * $P < 0.05$, ** $P < 0.01$ vs control

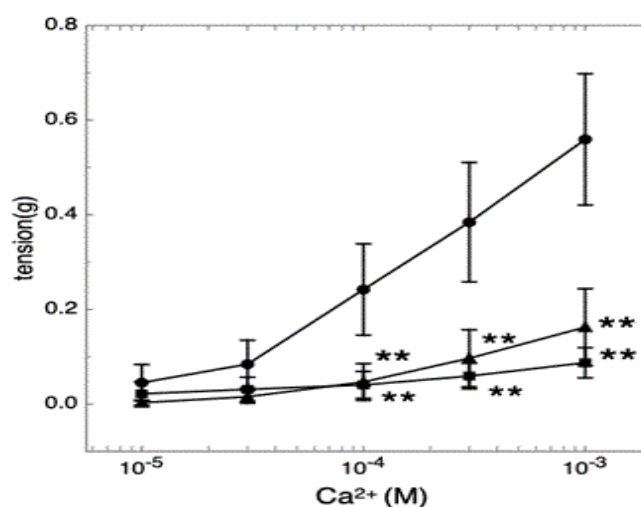


Figure 7: Concentration response relationships for contractile responses of aortic rings to Ca^{2+} in a Ca^{2+} -free medium preincubated with NE (10^{-6} M) and nicardipine (10^{-6} M). Symbols: -- control, -- CHWx 0.1 mg/mL, -- CHWx 0.3 mg/mL. Values represent mean $\pm$ SE of 4 determinations. ** $p < 0.01$ vs control

Discussion

CEAx (3 mg/mL) showed fast and slow vasorelaxations on NE-induced vasoconstrictions on aorta with endothelium. Focusing on the fast relaxation effect, this effect disappeared in de-endothelialized or pre-administration of 10^{-4} M LNMMA.

These results suggested that CEAx has nitric oxide (NO)-releasing effect dependent on the endothelium.

On the other hand, CHWx showed only slow and sustained vasorelaxant effects on NE-induced vasoconstrictions. This effect was also observed on endothelium removed aorta (data not shown). Then the effects of CHWx on aortic rings were thus independent of the presence of endothelium. To clarify the mechanisms of this relaxation effect, further experiments were examined. Pre-administration of CHWx showed no effect on NE-induced vasoconstriction (Figure 5). These results suggested that CHWx was thus considered to exert non-competitive inhibitory effects on adrenaline receptors.

We also examined the effects of CHWx on high potassium (60 mM) induced vasoconstriction. CHWx caused significant inhibition of Ca^{2+} -induced contraction in a Ca^{2+} -free, high potassium solution (Figure 6). These results indicate that CHWx inhibited Ca^{2+} influx via VDCs.

In addition, we examined the effects of CHWx to inhibit Ca^{2+} -induced contraction in aorta that had been pre-treatment with Ca^{2+} -free solution containing NE (10^{-6} M) and nicardipine (10^{-6} M). As shown in (Figure 7), CHWx inhibited the contraction significantly. These results indicate that CHWx exerts inhibitory effects on Ca^{2+} influx via ROCs, and the inhibition was more potent than VDCs.

In many cases, vasoconstrictor-induced contraction is mediated by Ca^{2+} influx. Given these findings, the vasorelaxant effect of

CHWx may be due to either the inhibition of Ca^{2+} influx via VDCs and ROCs or the inhibition of intracellular calcium signaling.

This study showed the biphasic vasorelaxant effects of extracts from the aerial part of coriander on rat aorta. Despite CEAx showed the endothelium dependent/independent vasorelaxant effects, CHWx remained only the endothelium-independent effects. Although the active ingredient is still unknown, the relatively low polarity component may act endothelium-dependent effect and the other high polarity component may possess an endothelium-independent effect. Coriander was rich in essential oils, but the major essential oil component, linalool, was not detected in either CEAx or CHWx. Jabeen et al. reported a vasorelaxant effect from coriander fruit aqueous-methanol extract, which may contain similar components in the aerial part. Hussain et al. reported the inhibitory effect of ACE from coriander leaf organic extracts and detected some flavonoids (e.g. quercetin, rutin, apigenin, luteolin and its glucosides) from active fraction [19, 20]. Flavonoids are contained in many plants and are known to have antioxidant actions, improving action against ischemic diseases, anti-inflammatory action, etc. [25]. Quercetin, apigenin, luteolin, and other flavonoids are reported to show vascular relaxation [26], luteolin and its dimethyl ether, quercetin glycosides, apigenin show NO-mediated vasorelaxant, atherogenesis-suppressing [27], luteolin reported that and potassium channel-opening effects [28].

Thus, we cleared that the physiological activities of these constituents in coriander contribute to the vasodilatory actions due to the antihypertensive effects. Furthermore, we revealed the unknown active components in coriander leaf which relate to the vasorelaxant effect.

Conclusion

The extracts of the aerial part of coriander (*Coriandrum sativum* L.) showed biphasic vasorelaxation (fast and slowly developing relaxations) on isolated rat aortic rings with endothelium. The fast vasorelaxant effect of ethyl acetate extract of coriander was attributed to NO-releasing dependent on endothelium. And the hot water extract of coriander showed slowly vasorelaxant activities attributed to blocking of Ca^{2+} influx via voltage-dependent Ca^{2+} channels (VDCs) and receptor-operated Ca^{2+} channels (ROCs).

Authors' contributions

TI and RO performed most of the experiments. JY and YW provided helpful advice during the research. TI designed the experiments.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on a responsible request.

Acknowledgment

The authors are grateful to Kinkoh-Seika Co., Ltd., (Yokohama, Japan) for the kindly donation of coriander samples. A part of this study was supported by the Pakti Academy Association. We are thankful to Mis Aina Miura and Hozumi Iida, students of Yokohama University of Pharmacy, for their helpful assistance. And also, we appreciate Prof. Nobuo Izumo for his kind advice.

Funding

Annual Research Grant from Yokohama University of Pharmacy

Conflict of interests

All authors declare that they have no competing interests.

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