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Investigating the Relaxing Effects of Coptis chinensis and Berberine on Lower Esophageal Sphincter Function: Potential Strategies for LES Motility Disorders

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Abstract

Achalasia, a primary motility disorder of the esophagus, is characterized by impaired relaxation of the lower esophageal sphincter (LES), resulting in symptoms such as difficulty swallowing, regurgitation, chest discomfort, and weight loss. Standard pharmacological treatments, including calcium channel blockers and nitrates, often provide limited benefit, highlighting the need for alternative therapeutic strategies. This study explores the effects of Coptis chinensis and its major bioactive constituent, berberine, on LES relaxation, aiming to identify new avenues for treatment. The relaxation effects of C. chinensis extract and berberine were tested on LES pre-contracted with carbachol, across varying concentrations. To uncover the mechanisms driving berberine-induced relaxation, several pharmacological inhibitors were applied, including tetrodotoxin, ω-conotoxin GVIA, rolipram, vardenafil, KT5823, KT5720, NG-nitro-L-arginine, tetraethylammonium (TEA), apamin, iberiotoxin, and glibenclamide.

Both C. chinensis extract and berberine produced robust, concentration-dependent relaxation of the LES. The effect of berberine was notably attenuated by TEA, suggesting that activation of potassium channels is a key mechanism underlying its action. The findings indicate that C. chinensis and berberine facilitate LES relaxation, primarily through potassium channel modulation. These results support the potential of these compounds as therapeutic agents for esophageal motility disorders, such as achalasia.

Keywords: Lower esophageal sphincter, Relaxation, Achalasia, Coptis chinensis, Berberine, Traditional Chinese medicine

Introduction

Achalasia is a rare disorder of esophageal motility, defined by the degeneration of inhibitory neurons in the distal esophagus and LES, leading to absent peristalsis and increased LES tone. The resulting inability of the LES to relax properly causes food retention in the lower esophagus and progressive symptoms, including dysphagia, regurgitation, chest pain, and weight loss. The disorder affects approximately 1–12 individuals per 100,000 annually [1]. Its etiology remains uncertain, with proposed factors including neuronal degeneration, viral triggers, genetic susceptibility, and autoimmune reactions [2]. Diagnosis generally relies on a combination of endoscopic evaluation, barium swallow studies, and esophageal manometry, while management strategies range from medications to endoscopic and surgical interventions [3].

Pharmacologic approaches for early-stage achalasia are limited in efficacy. Commonly prescribed agents such as nifedipine (10–30 mg sublingually) or nitrates (5 mg prior to meals) provide symptomatic relief but often incompletely and may lead to adverse effects [4]. These limitations underscore the importance of exploring alternative therapies with improved safety and effectiveness.

Traditional Chinese Medicine (TCM) has long been applied to gastrointestinal disorders, yet its role in achalasia remains underexplored. Among TCM herbs, Coptis chinensis (Huang Lian) has been widely used for digestive conditions. Its principal alkaloid, berberine,

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exhibits a broad spectrum of pharmacological activities, including antimicrobial, anti-inflammatory, metabolic, and anti-cancer properties [5–7].

Evidence suggests that C. chinensis and berberine can influence gastrointestinal motility. For example, C. chinensis demonstrates antinociceptive effects in animal models of irritable bowel syndrome, potentially by modulating serotonin and cholecystokinin pathways in the colon [8]. Berberine has been reported to suppress smooth muscle contractions in the gastrointestinal tract by inhibiting myosin light-chain kinase (MLCK), leading to reduced contraction amplitude in isolated duodenal and gastric strips, which may explain its antidiarrheal activity [9]. These observations imply a possible role for berberine in conditions characterized by altered smooth muscle tone, including achalasia.

Building on this background, the present study investigates whether C. chinensis extract and berberine can induce relaxation of the LES. We hypothesize that their effects are mediated via modulation of smooth muscle function, potentially involving ion channel regulation or intracellular signaling pathways. Understanding these mechanisms could offer novel, natural therapeutic strategies for achalasia, potentially improving efficacy while minimizing side effects associated with conventional medications.

Materials and Methods

Specimen collection and handling

Porcine tissues used in this investigation, from animals with an average weight of 110 kg, were obtained from abattoirs approved by the Council of Agriculture, Executive Yuan (Taiwan). The lower esophageal sphincter (LES) samples, consisting of portions of the distal esophagus and proximal stomach, were harvested from pigs not raised specifically for research purposes. These animals were humanely dispatched via electrical stunning followed by bleeding out. To maintain viability, the Krebs-Henseleit buffer employed here included 118 mM NaCl, 4.7 mM KCl, 1.2 mM NaH_2PO_4, 25 mM $NaHCO_3$, 1.8 mM $CaCl_2$, and 14 mM glucose, with the pH set to 7.4. The buffer was aerated for 15 minutes using a gas mixture of 95% O_2 and 5% CO_2 before application. Immediately following excision, the LES tissues were placed in cooled buffer and transferred to the lab within approximately 30 minutes to preserve their functional properties. This work did not require approval from the Institutional Animal Care and Use Committee at E-DA Hospital, since the esophageal and gastric tissues from pigs were regarded as edible materials rather than from living subjects, per applicable guidelines.

Preparation of coptis chinensis extract solution

The concentrated extract derived from the Chinese medicinal plant C. chinensis was supplied by Kaiser Pharmaceutical Co., Ltd. (Product No.: 8010, Batch No.: E12025, Tainan, Taiwan). For the experiments, 30 mg of the extract was dissolved in 1 ml of 20% ethanol to create the stock solution.

Assessment of relaxant activity

Impact of C. chinensis extract on carbachol-induced contraction in porcine LES

The porcine LES is an effective surrogate for human LES research owing to shared anatomic features and functional responses, such as similar muscular architecture and contraction patterns [10, 11]. Upon acquisition of LES tissues, encompassing the clasp and sling fiber components, the overlying mucosa was stripped away to expose these muscle layers. Strips of 1 cm × 0.5 cm were then cut from these muscles, tied with silk sutures, and suspended in a 5 ml organ bath filled with Krebs-Henseleit solution. The system was kept at 37 °C with ongoing gassing using 95% O_2 and 5% CO_2. Tension signals were captured via an isometric force transducer (FORT10g; Grass Technologies, RI, USA) linked to an amplifier (Gould Instrument Systems, OH, USA) and recorded on a computerized platform (BIOPAC Systems, CA, USA), with basal tension maintained at 1.0 g. This configuration facilitates investigation of LES physiology [10].

Muscle preparations were allowed to stabilize for 30 minutes initially, then contracted with 1 μM carbachol, followed by rinsing in fresh buffer. After a further 30-minute stabilization, a sustained contraction was elicited using 300 nM carbachol, which was designated as the 100% reference level. This dose was selected from dose-response experiments (ranging from 10 nM to 100 μM carbachol) as it exceeded the EC_{50} while preventing excessively intense contractions that could obscure relaxant actions.

The relaxant actions of C. chinensis extract at doses of 0.06, 0.24, and 0.6 g/L were then tested on both clasp and sling muscle preparations. These levels were achieved by introducing 10, 40, or 100 μL of the stock solution into the 5 ml bath volume. Dose selection was informed by

pilot experiments to span sub-effective to near-maximal responses.

Relaxant effects of berberine on carbachol-precontracted LES

This protocol evaluated berberine, a key alkaloid from Huang Lian, for its ability to induce LES relaxation. Using the established procedure, after the second equilibration phase and contraction with 300 nM carbachol, berberine was applied cumulatively at 10 µM, 30 µM, 100 µM, and 300 µM. These doses were chosen from preliminary trials to encompass a full range of relaxant potency. Berberine was purchased from Cayman Chemical (MI, USA).

Involvement of neural pathways in berberine-mediated LES relaxation

To determine if neural conduction contributes to berberine's relaxant effect on the LES, the experiment incorporated 1 µM tetrodotoxin (TTX), a blocker of voltage-gated sodium channels in nerves, and 1 µM ω-Conotoxin GVIA (CTX), an inhibitor of N-type calcium channels in neurons. These agents were introduced into the bath 15 minutes prior to adding 50 µM berberine [10].

Modulation of berberine-induced LES relaxation by agents affecting cAMP and cGMP pathways

The potential augmentation of berberine's relaxant action by elevating cyclic nucleotide levels was assessed using rolipram (1 µM, a selective PDE-4 inhibitor raising cAMP) or vardenafil (1 µM, a PDE-5 inhibitor elevating cGMP). Each was added to the bath 20 minutes before applying 50 µM berberine [10].

Contributions of cAMP, cGMP, and Nitric oxide to berberine-evoked LES relaxation

To clarify the participation of cyclic nucleotides and nitric oxide in berberine's mechanism, inhibitors were used: 1 µM KT5720 (PKA inhibitor), 1 µM KT5823 (PKG inhibitor), and 100 µM NG-nitro-L-arginine (L-NNA, NOS inhibitor). These compounds were administered 30 minutes before adding 50 µM berberine [10].

Examination of potassium channels in berberine-mediated LES relaxation

This protocol was designed to assess the contribution of potassium channels to the relaxant action of berberine on the LES. Various potassium channel antagonists were employed: 1 mM tetraethylammonium (TEA), a broad-spectrum potassium channel inhibitor; 100 nM apamin, which selectively blocks small-conductance Ca^{2+}-activated K^+ channels; 200 nM iberiotoxin (IbTX), specific for large-conductance Ca^{2+}-activated K^+ channels; and 10 µM glibenclamide, an inhibitor of ATP-sensitive K^+ channels. Consistent with the established procedure, each blocker was added to the bath 30 minutes prior to the application of 50 µM berberine [10, 12].

Statistical analysis

Results are expressed as means accompanied by the standard error of the mean (SEM). Comparisons were performed using either Student's t-test or one-way analysis of variance (ANOVA) with Tukey's post-hoc test, as appropriate. The minimum number of experiments per group was four. Statistical significance was defined as $p < 0.05$. All analyses were carried out with SPSS software version 24 (IBM Corp., NY, USA). Half-maximal effective concentration (EC_{50}) values were determined using GraphPad Prism version 5.

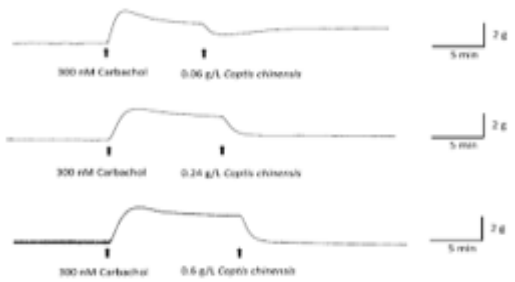
Results and Discussion

High-performance liquid chromatography (HPLC) profile of C. chinensis extract

Berberine served as the standard compound, with a detected retention time of 10.48 minutes.

Relaxant action of C. chinensis on carbachol-precontracted porcine LES

Representative recordings in **Figures 1a and 1b** illustrate the concentration-dependent relaxation produced by C. chinensis (0.06, 0.24, and 0.6 g/L) in sling and clasp muscle preparations, respectively. Both muscle types exhibited progressive relaxation with increasing extract concentrations **(Figures 1c and 1d)**. The degree of relaxation varied from 34.25% to 101.84% in sling fibers and from 56.38% to 105.14% in clasp fibers across the tested dose range (0.06–0.6 g/L). These responses differed significantly from those elicited by the vehicle alone (all $p < 0.05$; C. chinensis: $n \geq 4$, ethanol: $n \geq 3$). Moreover, the relaxant effects observed at 0.24 and 0.6 g/L were markedly greater than those at 0.06 g/L in both sling and clasp strips (all $p < 0.05$, $n \geq 4$).



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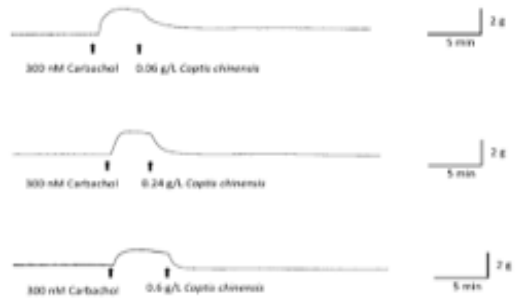

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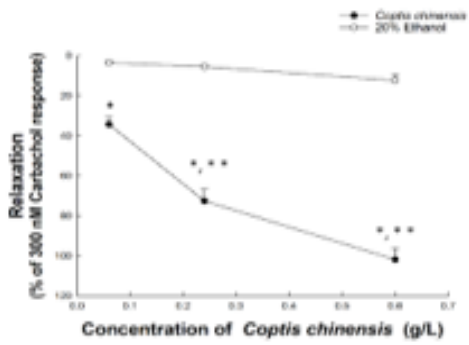

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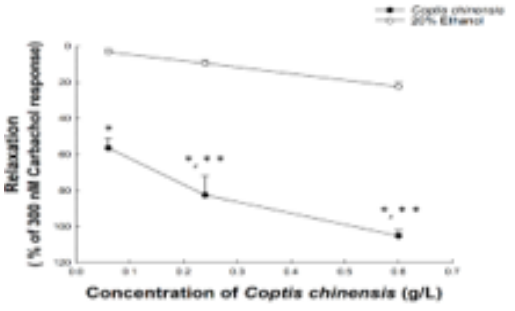

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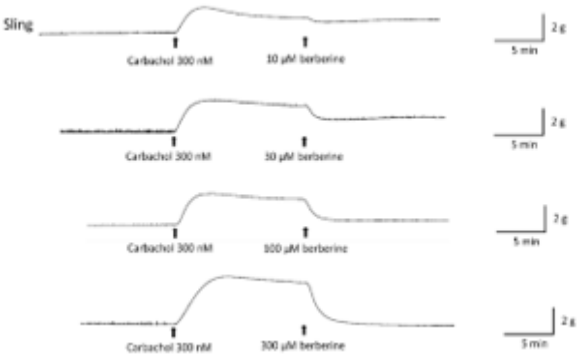
Figure 1. The image highlights the relaxant properties of an extract from Coptis chinensis on isolated porcine lower esophageal sphincter (LES) muscles, specifically the sling fibers (panel a) and clasp fibers (panel b), after these tissues were first contracted using 300 nM carbachol. Arrows denote the points where escalating doses of the herbal extract were applied. Panels c and d present the concentration-response curves for relaxation in sling and clasp muscles elicited by C. chinensis, benchmarked against a 20% ethanol vehicle control, and expressed as percent decreases relative to the contraction plateau induced by carbachol. Findings are based on no fewer than 4 independent tests with the extract and at least 3 with ethanol, including SEM as error bars. Symbols indicate statistical differences versus the matched ethanol control (*) or versus the effect of 0.06 g/L extract (**), with $p < 0.05$.

Relaxant actions of berberine, a key bioactive compound in C. chinensis, on the LES in a concentration-dependent manner

Here, we assessed how berberine—one of the main active alkaloids in C. chinensis—affects relaxation of the LES. All tests followed pre-contraction with 300 nM carbachol. Representative recordings in **Figure 2** (panels a for sling and b for clasp muscles) depict the relaxant responses to berberine applied at 10, 30, 100, and 300 µM, illustrating a marked escalation in relaxation as concentrations rose, in line with a concentration-dependent mechanism. Quantitative data for sling muscles **(Figure 2c)** revealed relaxation levels of 18.12 ± 1.01% (10 µM), 40.71 ± 1.04% (30 µM), 62.24 ± 3.94% (100 µM), and 91.96 ± 5.04% (300 µM). At 30 µM and 100 µM, these effects were statistically superior to vehicle controls ($p < 0.05$ each; $n = 4$). In clasp muscles **(Figure 2d)**, corresponding relaxations were 18.12 ± 2.12% (10 µM), 42.79 ± 3.87% (30 µM), 57.13 ± 4.22% (100 µM), and 96.28 ± 8.38% (300 µM), again showing significance over vehicle at 30 µM and 100 µM ($p < 0.05$; $n \geq 4$). Across both muscle types, the relaxations observed at 30, 100, and 300 µM markedly surpassed those at 10 µM ($p < 0.05$; $n = 4$). Collectively, these data suggest that berberine is largely responsible for the LES-relaxing activity of C. chinensis and could explain its possible benefits in managing disturbances of gut motility. The calculated EC50 for berberine in sling muscle was about 50 µM (across a tested range of 1 µM–1 mM), which matched the pattern seen in both fiber types, prompting the use of 50 µM berberine in follow-up studies on underlying mechanisms. For reliability, estradiol—a compound known from prior work to cause strong LES relaxation in porcine tissue [10]—was included as a positive control, whereas coptisine (another alkaloid from the same plant, found in initial tests to

produce negligible relaxation versus vehicle) acted as a negative control.



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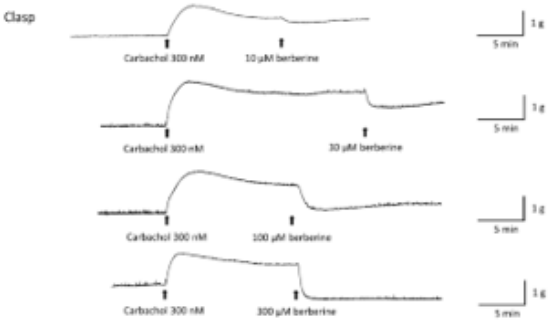

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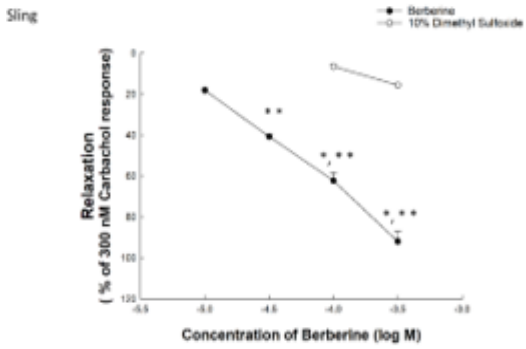

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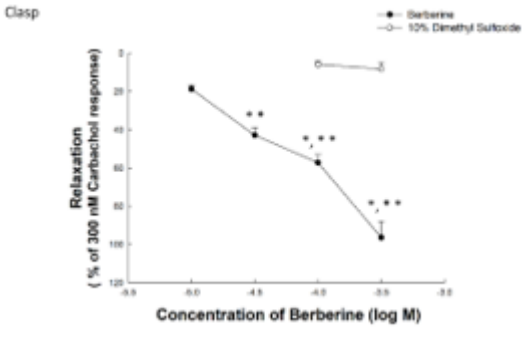

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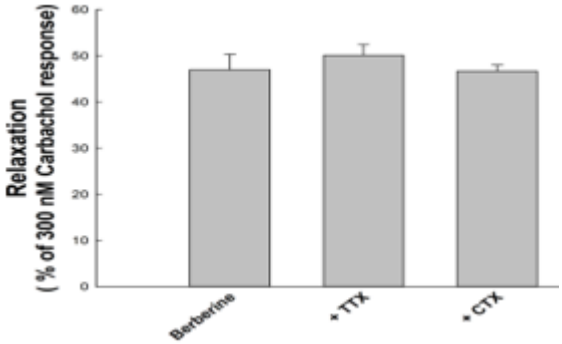
Figure 2. This illustration displays the relaxing actions of berberine on isolated porcine lower esophageal sphincter (LES) sling muscles (panel a) and clasp muscles (panel b), following initial contraction evoked by 300 nM carbachol, with arrows marking the application of carbachol itself and subsequent escalating concentrations of berberine. Panels c and d provide concentration-response data for berberine-mediated relaxation in sling and clasp fibers, evaluated relative to matched 10% DMSO vehicle controls, and reported as percentage reductions from the carbachol-established contractile baseline. Results stem from at least 4 independent experiments each for berberine and its corresponding DMSO control, with error bars denoting SEM. Markers highlight statistical significance compared to the relevant DMSO control (*) or versus the response to 10 μM berberine (**), at $p < 0.05$.

Impact of neural blockade on berberine-mediated relaxation in porcine sling muscle preparations

As depicted in **Figure 3a**, neither 1 μM tetrodotoxin (TTX) nor 1 μM ω-conotoxin (CTX) produced a notable alteration in the relaxation elicited by 50 μM berberine in sling strips ($p > 0.05$, $n = 4$).



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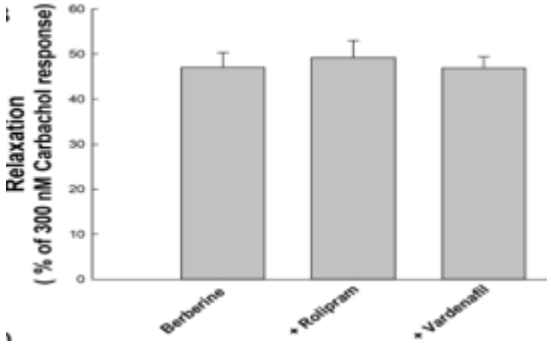

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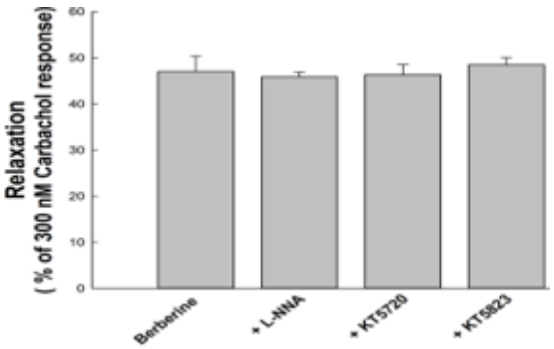

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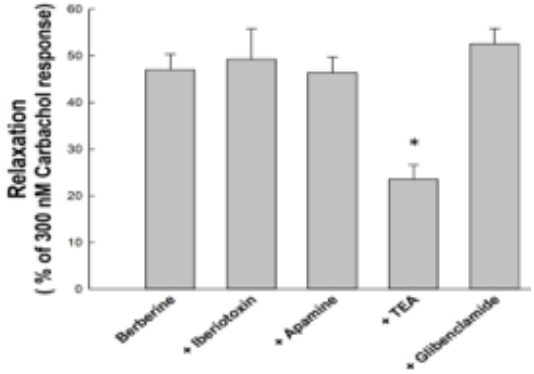

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Figure 3. This illustration outlines the influence of multiple pharmacological agents on the relaxation elicited by berberine in porcine lower esophageal sphincter (LES) tissue. Panel a reveals that neither tetrodotoxin (TTX) nor ω-conotoxin GVIA (CTX) produced a meaningful change in berberine-mediated relaxation ($p > 0.05$). Panel b indicates that rolipram and vardenafil likewise failed to substantially modify the relaxation response to berberine ($p > 0.05$). Panel c shows that NG-nitro-L-arginine (L-NNA), KT5823, and KT5720 exerted no notable influence on the relaxation ($p > 0.05$). In panel d, iberiotoxin (IbTX), apamin, and glibenclamide had no appreciable effect on berberine-induced relaxation ($p > 0.05$), whereas tetraethylammonium (TEA) markedly attenuated it ($p < 0.05$). Error bars denote SEM, and a single asterisk (*) denotes statistical significance relative to the relaxation produced by 50 µM berberine alone.

Investigation of cAMP and cGMP pathways in berberine-mediated relaxation of porcine sling muscle

As shown in **Figure 3b**, neither 1 µM rolipram nor 1 µM vardenafil augmented the relaxation of porcine sling preparations triggered by 50 µM berberine ($p > 0.05$, $n = 4$).

Evaluation of nitric oxide, cAMP, and cGMP involvement in berberine-mediated relaxation in porcine sling muscle

Figure 3c illustrates that pretreatment with 100 µM L-NNA, 1 µM KT5823, or 1 µM KT5720 did not diminish the relaxation evoked by 50 µM berberine in porcine sling strips ($p > 0.05$, $n = 4$).

Contribution of potassium channels to relaxation induced by C. chinensis and berberine in porcine sling muscle

Data in **Figure 3d** indicate that 100 nM apamin ($n = 4$), 200 nM iberiotoxin (IbTX; $n = 5$), and 10 µM glibenclamide ($n = 4$) failed to suppress the relaxation of porcine sling strips caused by 50 µM berberine ($p > 0.05$). In contrast, 1 mM tetraethylammonium (TEA) substantially attenuated this relaxation response ($p < 0.05$, $n = 4$).

The present work establishes that Coptis chinensis extract potently induces relaxation of the LES. Earlier studies have documented the influence of C. chinensis on motility and overall function throughout the gastrointestinal tract. It has proven efficacious in reducing visceral hypersensitivity associated with irritable bowel syndrome [8], supporting improved digestive performance when combined with Dolomiaea souliei [13], and modulating immune responses and metabolic processes depending on preparation methods [14]. Moreover, it strengthens intestinal barrier integrity in models of ulcerative colitis [15].

Berberine, the prominent yellow alkaloid derived from C. chinensis, is well recognized for its antimicrobial and anti-inflammatory activities. Traditionally employed as a textile dye [16], it has more recently exhibited promise against atherosclerosis via pathways involving lipid modulation, lowering of blood pressure and glucose levels, suppression of inflammation, and restraint of vascular smooth muscle proliferation [17]. Berberine also displays vasorelaxant and antiproliferative characteristics [18], underscoring its wide-ranging pharmacological utility.

A key focus of contemporary investigation centers on berberine's modulation of the intestinal microbiome, with important therapeutic ramifications for conditions such as diabetes, hyperlipidemia, atherosclerosis, and hepatic disorders [19]. Its broader effects on metabolism further position it as a candidate for addressing obesity and certain neurodegenerative conditions [20].

In our investigation, berberine not only exhibited a relaxant effect on the lower esophageal sphincter (LES), but also exerted substantial effects on gastrointestinal motility. It achieves this modulation by inducing relaxation in rat gastric fundus strips via blockade of calcium influx [21], diminishing contractile responses in gastrointestinal smooth muscle [9], and displaying beneficial outcomes in irritable bowel syndrome through suppression of colonic smooth muscle neurotransmission [22]. Additionally, berberine attenuates intestinal myoelectric activity and peristaltic transit, possibly through involvement of opioid and α-adrenergic receptors [23], while also interfering with both extracellular and intracellular Ca2+ fluxes in colonic smooth muscle cells [24]. Of particular importance among these actions are berberine's antidiarrheal benefits, as supported by a systematic review and meta-analysis that confirmed its effectiveness and safety for managing diarrhea in pediatric and adult populations [25]. Collectively, these observations position berberine as a promising multifaceted therapeutic agent for various gastrointestinal conditions.

Smooth muscle relaxation involves intricate signaling cascades. To clarify the pathways responsible for berberine-mediated relaxation in porcine LES smooth muscle, we applied a series of pharmacological tools aimed at examining possible neural involvement as well as routes linked to cyclic nucleotides, nitric oxide, and potassium channels [26]. This thorough mechanistic exploration yields important clues regarding berberine's operational mode.

To probe whether neural elements contribute to berberine-evoked LES relaxation in porcine tissue, we utilized tetrodotoxin (TTX) and charybdotoxin (CTX). The lack of any inhibitory effect from these agents is noteworthy, indicating that berberine's relaxant action on the porcine LES occurs independently of neural mediation.

We tested rolipram and vardenafil, selective inhibitors of phosphodiesterase-4 (PDE-4) and phosphodiesterase-5 (PDE-5), respectively. These compounds elevate intracellular cAMP and cGMP concentrations, which could augment smooth muscle relaxation [7, 27]. Nevertheless, neither agent potentiated berberine's relaxant influence on the porcine LES. Likewise, the cAMP-dependent protein kinase inhibitor KT5720 and the cGMP-dependent protein kinase inhibitor KT5823 failed to alter berberine-induced relaxation in the LES. These data imply that cyclic nucleotide pathways (cAMP or cGMP) and nitric oxide signaling are not implicated in berberine's mechanism [10]. Consistent with this, L-NNA, an inhibitor of nitric oxide synthase, did not interfere with berberine-triggered LES relaxation, further confirming that nitric oxide generation plays no role in this process.

We also assessed potassium channel involvement in berberine-induced porcine LES relaxation employing targeted blockers, including iberiotoxin (IbTX), apamin, tetraethylammonium (TEA), and glibenclamide. Strikingly, TEA-mediated potassium channel blockade markedly attenuated the relaxant response in porcine LES tissue [10, 12]. In contrast, apamin, iberiotoxin, and glibenclamide produced no significant changes in berberine-evoked relaxation. Taken together, these outcomes point to potassium channels as the principal mediators of berberine's LES-relaxing effect. Subsequent investigations might focus on pinpointing the precise subtype of TEA-sensitive channels and delineating any upstream regulatory signals that activate them.

These results distinguish berberine's mode of action from that of standard achalasia pharmacotherapies. For instance, nifedipine relaxes muscle by blocking calcium entry into cells, whereas nitrates elevate nitric oxide concentrations [1]. Berberine, however, primarily promotes LES relaxation through potassium channel opening, without reliance on cAMP, cGMP, or nitric oxide routes. This unique profile could translate to fewer systemic adverse effects compared with existing options.

Studies on traditional Chinese medicine (TCM) and natural products have illuminated their influences on LES dynamics and esophageal performance. The Modified Xiaochaihu Decoction elevates LES pressure while decreasing ineffective swallows, indicating utility in gastroesophageal reflux disease management [28]. Extracts from Arecae pericarpium, especially arecoline, provoke concentration-dependent LES contractions [29]. Ginger has been found to leave LES basal pressure and esophageal contractile patterns unchanged, yet it promotes LES relaxation and slows contraction propagation, which may facilitate gas clearance [30]. The ginger component 6-gingerol elevates LES tone [31]. Extract of Curcumae longae Rhizoma mitigates esophageal injury and reduces inflammatory markers in models of acute reflux esophagitis [32]. Peppermint oil, recognized for its smooth muscle-relaxing properties, provides relief in diffuse esophageal spasm [33]. Such evidence broadens knowledge of how traditional remedies modulate LES function.

The relaxant actions of Coptis chinensis and berberine on the LES, as revealed here, introduce novel avenues for managing gastrointestinal disturbances, integrating TCM principles with contemporary pharmacological understanding. The established potassium channel-dependent mechanism opens possibilities for more precise therapeutic interventions. Although potassium channel modulators are not yet commonplace in gastrointestinal therapeutics, their efficacy has been documented in cardiovascular and neurologic applications [34–36]. This pathway may extend to additional smooth muscle pathologies [37] and support tailored approaches for LES-related conditions, fostering innovative research in gastroenterology.

This preliminary work offers foundational evidence supporting the therapeutic promise of Coptis chinensis and berberine in LES dysfunctions. Nonetheless, reliance on ex vivo porcine LES preparations constrains broader interpretations of their in vivo behavior. To overcome these constraints and strengthen translational relevance, we recommend supplementing with in vitro cellular models and in vivo animal experiments. Such steps would elucidate molecular details, toxicity profiles, pharmacokinetic/pharmacodynamic properties, and overall safety. Human clinical trials remain critical to verify LES relaxation in patients and evaluate therapeutic benefits for motility disorders. Upcoming efforts should address optimal dosing and delivery strategies, long-term tolerability and effectiveness, broader impacts on gastrointestinal motility issues, and possible synergistic combinations. Moreover, examining other bioactive components in Coptis chinensis could uncover additional contributors to LES relaxation and their mechanisms. Pursuing these directions will advance the creation of superior therapies for gastrointestinal motility problems, providing renewed options for individuals suffering from disorders like achalasia.

Conclusion

The present investigation demonstrates pronounced relaxant actions of Coptis chinensis and its active compound berberine on the LES. Berberine's effect appears to depend predominantly on potassium channel activation, offering a plausible explanation for these agents' activity. These discoveries lay groundwork for ongoing exploration aimed at designing mechanism-based therapies for gastrointestinal motility disturbances, including achalasia, leveraging these compounds and their identified pathways.

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Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Vaezi MF, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG clinical guidelines: diagnosis and management of Achalasia. Am J Gastroenterol. 2020;115(9):1393–411. https://doi.org/10.14309/ajg.0000000000000731.
2. Gyawali CP. Achalasia: new perspectives on an old disease. Neurogastroenterol Motil. 2016;28(1):4–11. https://doi.org/10.1111/nmo.12750.
3. Zaninotto G, Bennett C, Boeckxstaens G, Costantini M, Ferguson MK, Pandolfino JE, et al. The 2018 ISDE achalasia guidelines. Dis Esophagus. 2018. https://doi.org/10.1093/doy071.
4. Vaezi MF, Richter JE. Current therapies for achalasia: comparison and efficacy. J Clin Gastroenterol. 1998;27(1):21–35. https://doi.org/10.1097/00004836-199807000-00006.
5. Meng G, Li P, Du X, Feng X, Qiu F. Berberine alleviates ulcerative colitis by inhibiting inflammation through targeting IRGM1. Phytomedicine. 2024;133:155909. https://doi.org/10.1016/j.phymed.2024.155909.
6. Song D, Hao J, Fan D. Biological properties and clinical applications of berberine. Front Med. 2020;14(5):564–82. https://doi.org/10.1007/s11684-019-0724-6.
7. Liu L, Li J, He Y. Multifunctional epiberberine mediates multi-therapeutic effects. Fitoterapia. 2020. https://doi.org/10.1016/104771.
8. Tjong Y, Ip S, Lao L, Fong HH, Sung JJ, Berman B, Che C. Analgesic effect of Coptis chinensis rhizomes (Coptidis Rhizoma) extract on rat model of irritable bowel syndrome. J Ethnopharmacol. 2011;135(3):754–61. https://doi.org/10.1016/j.jep.2011.04.007.

9. Xu Z, Zhang M, Dou D, Tao X, Kang T. Berberine Depresses Contraction of Smooth Muscle via inhibiting myosin light-chain kinase. Pharmacogn Mag 2017 Jul-Sep;13(51):454–58. https://doi.org/10.4103/pm.pm_205_16
10. Tsai CC, Tey SL, Chang LC, Su YT, Lin KJ, Huang SC. Estradiol mediates relaxation of porcine lower esophageal sphincter. Steroids. 2018;136:56–62. https://doi.org/10.1016/j.steroids.2018.05.001.
11. Farré R, Aulí M, Lecea B, Estrada O, Suñol X, Clavé P. Mechanisms controlling function in the clasp and sling regions of porcine lower oesophageal sphincter. Br J Surg. 2007;94(11):1427–36. https://doi.org/10.1002/bjs.5831.
12. Weatherall KL, Goodchild SJ, Jane DE, Marrion NV. Small conductance calcium-activated potassium channels: from structure to function. Prog Neurobiol. 2010;91(3):242–55. https://doi.org/10.1016/j.pneurobio.2010.03.002.
13. Wang T, Zhang C, Li H, Zhou R, Ye X, Yang Y, et al. The underlying rationality of Chinese medicine herb pair Coptis chinensis and Dolomiaea souliei: from the perspective of metabolomics and intestinal function. J Ethnopharmacol. 2022. https://doi.org/10.1016/115065.
14. Wang YX, Zhang JY, Cao YM, Liu T, Zhang ZK, Zhang BX, Feng WS, Li K, Zheng XK, Zhou N. Coptis chinensis-induced changes in metabolomics and gut microbiota in rats. Am J Chin Med. 2023;51(6):1547–76. https://doi.org/10.1142/S0192415X23500702.
15. Xie Q, Li H, Ma R, Ren M, Li Y, Li J, Chen H, Chen Z, Gong D, Wang J. Effect of Coptis chinensis franch and Magnolia officinalis on intestinal flora and intestinal barrier in a TNBS-induced ulcerative colitis rats model. Phytomedicine. 2022;97:153927. https://doi.org/10.1016/j.phymed.2022.153927.
16. Pirillo A, Catapano AL. Berberine, a plant alkaloid with lipid- and glucose-lowering properties: from in vitro evidence to clinical studies. Atherosclerosis. 2015;243(2):449–61. https://doi.org/10.1016/j.atherosclerosis.2015.09.032.
17. Wu M, Wang J, Liu LT. Advance of studies on anti-atherosclerosis mechanism of berberine. Chin J Integr Med. 2010;16(2):188–92. https://doi.org/10.1007/s11655-010-0188-7.
18. Ko WH, Yao XQ, Lau CW, Law WI, Chen ZY, Kwok W, Ho K, Huang Y. Vasorelaxant and antiproliferative effects of berberine. Eur J Pharmacol. 2000;399(2–3):187–96. https://doi.org/10.1016/s0014-2999(00)00339-3.
19. Yang F, Gao R, Luo X, Liu R, Xiong D. Berberine influences multiple diseases by modifying gut microbiota. Front Nutr. 2023;10:1187718. https://doi.org/10.3389/fnut.2023.1187718.
20. Gasmi A, Asghar F, Zafar S, Oliinyk P, Khavrona O, Lysiuk R, et al. Berberine: pharmacological features in health, disease and aging. Curr Med Chem. 2024;31(10):1214–34. https://doi.org/10.2174/0929867330666230207112539.
21. Lin WC, Chang HL. Relaxant effects of berberine on the rat fundus. Res Commun Mol Pathol Pharmacol. 1995;90(3):333–46.
22. Lu Y, Huang J, Zhang Y, Huang Z, Yan W, Zhou T, Wang Z, Liao L, Cao H, Tan B. Therapeutic effects of Berberine Hydrochloride on stress-Induced Diarrhea-Predominant irritable bowel syndrome rats by inhibiting neurotransmission in Colonic smooth muscle. Front Pharmacol. 2021;12:596686. https://doi.org/10.3389/fphar.2021.596686.
23. Eaker EY, Sninsky CA. Effect of berberine on myoelectric activity and transit of the small intestine in rats. Gastroenterology. 1989;96:1506–13.
24. Cao JW, Luo HS, Yu BP, Huang XD, Sheng ZX, Yu JP. Effects of berberine on intracellular free calcium in smooth muscle cells of Guinea pig colon. Digestion. 2001;64:179–83.
25. Yu M, Jin X, Liang C, Bu F, Pan D, He Q, et al. Berberine for diarrhea in children and adults: a systematic review and meta-analysis. Ther Adv Gastroenterol. 2020. https://doi.org/10.1177/1756284820961299.
26. Murthy KS. Signaling for contraction and relaxation in smooth muscle of the gut. Annu Rev Physiol. 2006;68:345–74. https://doi.org/10.1146/annurev.physiol.68.040504.094707.
27. Ribeiro ASF, Fernandes VS, Martínez-Sáenz A, Martínez P, Barahona MV, Orensanz LM, et al. Powerful relaxation of phosphodiesterase type 4 inhibitor rolipram in the pig and human bladder neck. J Sex Med. 2014;11(4):930–41. https://doi.org/10.1111/jsm.12456.
28. Li Z, Tao L, Zhang SS, Sun XH, Chen SN, Wu J. Modified Xiaochaihu Decoction for gastroesophageal reflux disease: a randomized

double-simulation controlled trial. World J Gastroenterol. 2021;27:4710–21. https://doi.org/10.3748/wjg.v27.i28.4710.

29. Tey SL, Li CY, Lin LW, Chang LC, Chen YL, Chang FR, Yang SN, Tsai CC. Arecae pericarpium extract induces porcine lower-esophageal-sphincter contraction via muscarinic receptors. BMC Complement Med Ther. 2021;21:275. https://doi.org/10.1186/s12906-021-03442-8. PMID: 34736444.
30. Lohsiriwat S, Rukkiat M, Chaikomin R, Leelakusolvong S. Effect of ginger on lower esophageal sphincter pressure. J Med Assoc Thail. 2010;93:366–72.
31. Promdam N, Khuituan P, Panichayupakaranant P. Effects of standardized [6]-gingerol extracts and [6]-gingerol on isolated ileum and lower esophageal sphincter contractions in mice. Food Chem. 2022;378:132077. https://doi.org/10.1016/j.foodchem.2022.132077.
32. Lee JA, Shin MR, Kim MJ, Lee JH, Park HJ, Roh SS. Protective effects of inflammation of Curcumae Longae Rhizoma 30% EtOH extract on Acute Reflux Esophagitis rats. BioMed Res Int. 2021. https://doi.org/10.1155/8854945.
33. Scarpellini E, Broeders B, Schol J, Santori P, Addarii M, Boccuto L, Carbone F, Abenavoli L, Tack J. The Use of Peppermint Oil in Gastroenterology. Curr Pharm Des. 2023;29:576–83. https://doi.org/10.2174/138161282966623032816 3449.
34. Maqoud F, Scala R, Hoxha M, Zappacosta B, Tricarico D. ATP-sensitive Potassium Channel subunits in Neuroinflammation: Novel Drug targets in neurodegenerative disorders. CNS Neurol Disord Drug Targets. 2022;21(2):130–49. https://doi.org/10.2174/187152732066621011909 5626.
35. Naffaa MM, Al-Ewaidat OA. Ligand modulation of KCNQ-encoded (KV7) potassium channels in the heart and nervous system. Eur J Pharmacol. 2021;906:174278. https://doi.org/10.1016/j.ejphar.2021.174278.
36. Grunnet M, Strøbæk D, Hougaard C, Christophersen P. Kv7 channels as targets for anti-epileptic and psychiatric drug-development. Eur J Pharmacol. 2014;726:133–7. https://doi.org/10.1016/j.ejphar.2014.01.017.
37. Tutuian R, Castell DO. Esophageal motility disorders (distal esophageal spasm, nutcracker esophagus, and hypertensive lower esophageal sphincter): modern management. Curr Treat Options Gastroenterol. 2006;9(4):283–94. https://doi.org/10.1007/s11938-006-0010-y.