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Uterorelaxant Activity of *Laurus nobilis* L. Leaf Extract on Mouse Uterine Contractility

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ABSTRACT

Background: The leaves of *Laurus nobilis* are traditionally used in folk medicine for their anti-inflammatory, antinociceptive, muscle relaxant properties and relief of menstrual pain. The effect of *L. nobilis* on uterine contractility remains poorly understood. This study investigated the relaxant effects of *Laurus nobilis* leaf extract (LNE) on isolated non-pregnant mouse uterus and explored its possible underlying mechanisms.

Methods: The effects of increasing concentrations of LNE (6.25–400 µg/mL) on spontaneous contractions and contractions induced by oxytocin, prostaglandin $F_2\alpha$ ($PGF_2\alpha$), methacholine, high potassium chloride (KCl), and oxytocin in calcium-free medium were evaluated. Additional experiments were performed in the presence of propranolol or tetraethylammonium.

Results: LNE significantly reduced spontaneous uterine contractions in a concentration-dependent manner. The extract significantly suppressed uterine contractions induced by oxytocin, $PGF_2\alpha$, methacholine, and high KCl. The inhibitory effect was not attenuated by propranolol or tetraethylammonium.

Conclusion: These findings demonstrate that LNE possesses significant uterorelaxant activity in the isolated nonpregnant mouse uterus, possibly mediated through inhibition of extracellular calcium influx. These findings support the potential pharmacological relevance of *L. nobilis* in the management of conditions associated with excessive uterine contractility, such as dysmenorrhea.

Keywords: calcium influx, *Laurus nobilis*, non-pregnant, uterine contractility, uterorelaxant

1. INTRODUCTION

Dysmenorrhoea is a common gynecological condition among menstruating women of reproductive age and is often associated with significant emotional, psychological, and functional health burdens [1]. Excessive production of uterine prostaglandins is considered a major contributor to the condition, leading to increased uterine contractility and menstrual pain [2, 3]. In many developing countries, traditional medicinal plants remain widely used for the management of various health conditions [4]. Among these medicinal plants is *Laurus nobilis*, which has gained attention for its potential therapeutic effects in the management of dysmenorrhoea. A single-blind randomized standard-controlled clinical study evaluating the efficacy of *L. nobilis* in the management of primary dysmenorrhoea was conducted at the NIUM Hospital, Bengaluru [5, 6], suggesting its potential usefulness in relieving menstrual pain. *L. nobilis*, (bay laurel or sweet bay), a member of the Lauraceae family, is an aromatic plant. It is a perennial shrub or small tree native to the Mediterranean region and widely distributed in temperate and warm climates [6, 7]. *L. nobilis* leaves are used either fresh or dried in the food and pharmaceutical industries to enhance the flavor of various culinary dishes such as seasoning meat, fish, vegetables and its aromatic essential oil is widely utilized in perfumery for fragrance production [8]. Phytochemical investigations of *L. nobilis* leaves have revealed the presence of numerous bioactive constituents, including monoterpenes, sesquiterpenes, fatty acids, flavonoids, phenolic acids, and various minerals. The major volatile components of the leaf extract include 1,8-cineole, methyleugenol, α-terpinyl acetate, α-pinene, β-pinene, sabinene, and linalool, with 1,8-cineole being one of the principal constituents [9,10]. These bioactive compounds contribute to the diverse pharmacological activities reported for bay leaves, including antioxidant, antimicrobial, antidiabetic, anti-ulcerogenic, neuroprotective, antiproliferative, antinociceptive, anti-inflammatory, and anticholinergic properties [11]. Previous studies have reported smooth muscle relaxant effects of *L. nobilis* in gastrointestinal and vascular tissues

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[12, 13]. However, the direct effects on uterine smooth muscle contractility have not been well investigated. This study aimed to investigate the effect of *L. nobilis* leaf extract on isolated non-pregnant mouse uterus and to elucidate its possible underlying mechanisms.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Biological materials

Dried leaves of *L. nobilis* were obtained from Uselu market, Edo State, Nigeria, and authenticated at the Herbarium Unit, Department of Plant Biology and Biotechnology, University of Benin, where a voucher specimen (UBH-L300) was deposited. Thirty non-pregnant female Swiss mice (8 – 10 weeks old) were obtained from the Animal Facility of the Department of Pharmacology and Toxicology, University of Benin. Animals were maintained under standard laboratory conditions (24 ± 2°C) with a natural light-dark cycle and had *ad libitum* access to food and water. All procedures were conducted in accordance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals [14].

2.1.2 Chemicals and reagents

Oxytocin was obtained from Anhui Hongye Pharmaceutical Co., Ltd. (China). Methacholine chloride, Tetraethylammonium, and propranolol were obtained from Sigma-Aldrich (UK). Prostaglandin $F_2\alpha$ ($PGF_2\alpha$) was obtained from Bioveta (Czech Republic). Physiological saline solution (PSS) components including Sodium Chloride (NaCl), Potassium Chloride (KCl), D-Glucose, Sodium Bicarbonate ($NaHCO_3$), and Calcium Chloride ($CaCl_2$) were of analytical grade and sourced from Guangdong Guanghua Sci-Tech Co. Ltd. (China) and Sigma-Aldrich (UK). Other reagents included ethanol (Pharmatrends, Nigeria), methylene blue (Tianjin Kermel Chemical Reagent Co., Ltd., China), and ethylenediaminetetraacetic acid (EDTA) (Guangdong Guanghua Sci-Tech Co., Ltd., China).

2.2 Methods

2.2.1 Extraction of plant material

The dried leaves of *L. nobilis* were pulverized and 543.5 g of the powder was extracted with a hydro-ethanol mixture (1:1) using a Soxhlet extraction apparatus. The extract obtained was concentrated using a rotary evaporator at 60°C to obtain the crude *L. nobilis* extract (LNE), with a percentage yield of 19.94% w/w. The extract was then stored at 4°C until use.

2.2.2 Preparation of uterine tissue

On the day of the experiment, vaginal cytology was performed to identify mice in the estrus phase, characterized by predominance of cornified epithelial cells [15]. Vaginal smears were obtained by flushing the vaginal lumen with 0.1 mL normal saline. The samples were transferred onto glass slides, air-dried, fixed with cold methanol, and stained with 0.1% methylene blue. Slides were examined under a microscope (VisiScope VWR, UK). Mice in estrus were euthanized by cervical dislocation, and uterine horns were excised and placed in a warm aerated PSS. Tissues were cleaned of connective tissue and cut into 1 - 2 mm segments. Each segment was mounted vertically in a 10 mL organ bath containing PSS maintained at 37ºC and continuously aerated with 100% oxygen. One end of the tissue was fixed to a tissue holder, while the other was connected to an isometric force transducer (PanLab, ADInstruments, Spain). Contractile activity was recorded using a PowerLab data acquisition system (Model ML826, ADInstruments, Spain) with LabChart software (MLS060/8 version 8.0, ADInstruments, Spain). A resting tension of 0.5 g was applied and tissues were allowed to equilibrate for 30 – 35 min before experimentation [16].

2.2.3 Effect of LNE on spontaneous uterine contractions

Following equilibration, spontaneous uterine contractions were recorded for 10 min and taken as the control (100% contraction). LNE (6.25 – 400 µg/mL) was added cumulatively at 5-min intervals. Changes in amplitude and frequency of contractions were recorded, After the final concentration, tissues were washed with fresh PSS to allow recovery.

2.2.4 Effect of LNE on uterine contractions induced by oxytocin

Uterine strips were precontracted with oxytocin (14 nM), after which cumulative concentrations of LNE (6.25 – 400 µg/mL) were added at 5-min intervals. Contractile responses were recorded and vehicle controls were performed using distilled water.

2.2.5 Effect of LNE on uterine contractions induced by prostaglandin $F_2\alpha$
To evaluate the effect of LNE on prostaglandin-induced contractions, uterine tissues were precontracted with $PGF_2\alpha$ (10^{-6} M). LNE (6.25 – 400 µg/mL) was added cumulatively at 5-min intervals and changes in contractile activity were recorded. Control experiments were performed using the vehicle (distilled water).

2.2.6 Effect of LNE on uterine contractions induced by high-KCl
Uterine strips were depolarized with high-KCl (80 mM) to induce sustained tonic contraction. LNE (6.25 – 400 µg/mL) was then added cumulatively at 5-min intervals and inhibitory responses were recorded.

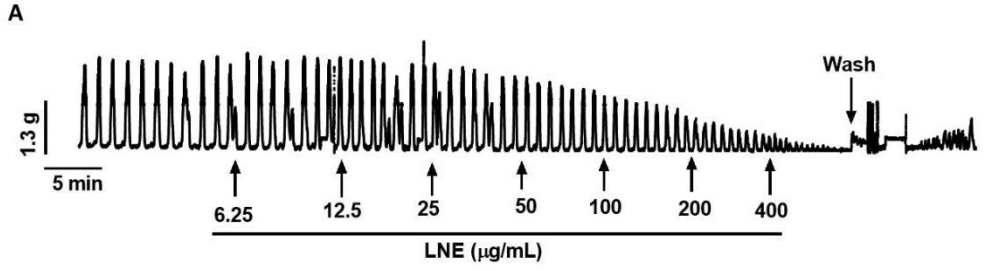
2.2.7 Effect of LNE on oxytocin-induced contractions in calcium-free medium
To assess the role of intracellular calcium release, experiments were performed in calcium-free PSS containing EDTA (0.1 mM). After spontaneous activity ceased, oxytocin (14 nM) was added to induce contractions mediated by intracellular calcium release. LNE (400 µg/mL) was subsequently added and changes in contractile activity were recorded.

2.2.8 Effect of LNE on uterine contractions induced by methacholine
To determine whether the inhibitory effects of LNE involves muscarinic receptors, uterine strips were stimulated with methacholine (MCh, 10 µM). LNE (6.25 – 400 µg/mL) was then added cumulatively without washing at 5-min intervals, and contractile responses were recorded.

2.2.9 Effect of LNE in the presence of antagonists
To investigate possible mechanisms underlying the inhibitory effects of LNE on uterine contractility, experiments were performed in the presence of tetraethylammonium (TEA, 5 mM, a non-selective potassium channel blocker), and propranolol (20 µM, a non-selective β-adrenergic receptor antagonist). Each antagonist was added to the isolated uterine tissue and allowed to equilibrate for 5 min before the cumulative addition of LNE (6.25 – 400 µg/mL). Control experiments were performed using distilled water.

2.3 Data analysis
Contractile parameters analyzed include amplitude, frequency and area under the curve (AUC). Amplitude and AUC were measured over 5-min periods before and after treatment, while frequency was determined by counting the number of contractions occurring within 5 min [17]. Data are expressed as mean ± standard error of the mean (SEM), where n represents the number of animals used. Statistical comparisons were performed using one-way analysis of variance (ANOVA) followed by Dunnett's post hoc test, with $p < 0.05$ considered statistically significant. Concentration-response curves and the half-maximal inhibitory concentration (IC_{50}) values were determined using nonlinear regression. All statistical analyses were performed using GraphPad Prism version 8.1 (San Diego, CA, USA).

3. RESULTS
3.1 Effect of LNE on spontaneous uterine contractility.
Cumulative administration of LNE (6.25 – 400 µg/mL) produced a concentration-dependent inhibition of spontaneous uterine contractions in isolated uterine strips from non-pregnant mice (Figure 1A - D). At lower concentrations (6.25 – 100 µg/mL), only slight reductions in contraction amplitude were observed. However, significant inhibition occurred at 200 µg/mL ($P < 0.05$), while complete suppression of contractile activity was achieved at 400 µg/mL ($P < 0.001$). In contrast, contraction frequency remained largely unchanged across the tested concentrations. The calculated IC_{50} values for inhibition of contraction amplitude, frequency, and AUC were 92.48 µg/mL, 109.20 µg/mL and 69.07 µg/mL, respectively. Following the washout with fresh PSS, spontaneous contractions recovered rapidly.



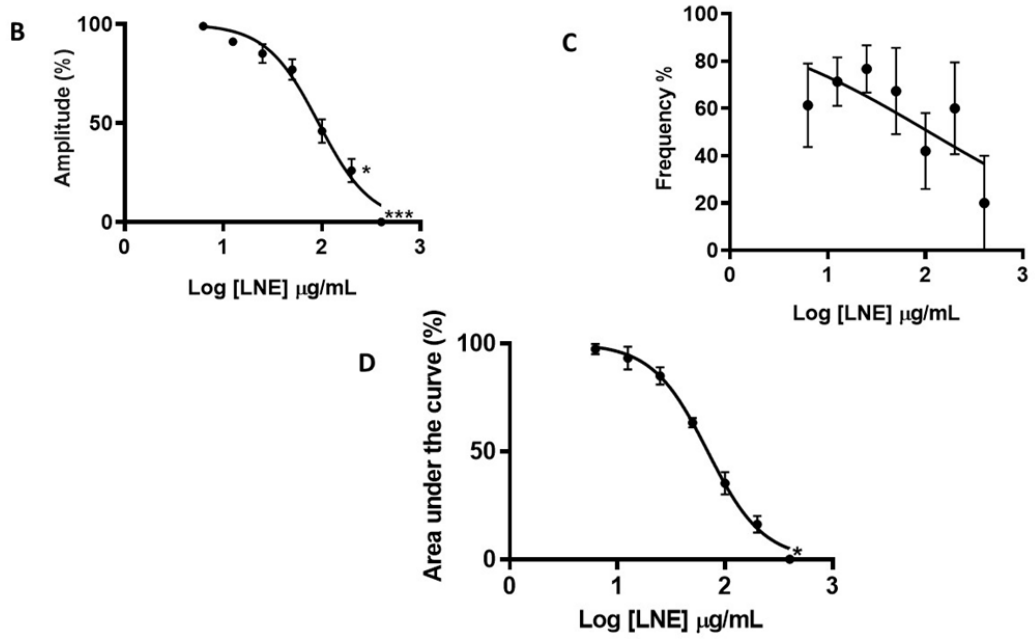


Figure 1. Effect of LNE on spontaneous uterine contractions in non-pregnant mice. (A) Recording of the effect of cumulative concentrations of LNE (6.25 – 400 µg/mL) on spontaneous uterine contractions in non-pregnant mice. Concentration-response curves showing the effects of LNE on the spontaneous contraction amplitude (B), frequency (C) and area under the curve (D). n = 5 animals. *P < 0.05, ***P < 0.001, compared to control

3.2 Effect of LNE on uterine contractions induced by oxytocin.

Oxytocin (14 nM) markedly increased the amplitude and frequency of uterine contractions (Figure 2A). Subsequent cumulative addition of LNE (6.25 - 400 µg/mL) produced a gradual reduction in oxytocin-induced contractile activity (Figure 2B). Although reductions in amplitude and frequency were modest, LNE significantly decreased overall contractile activity, as reflected by a reduction in AUC (Figure 2C).

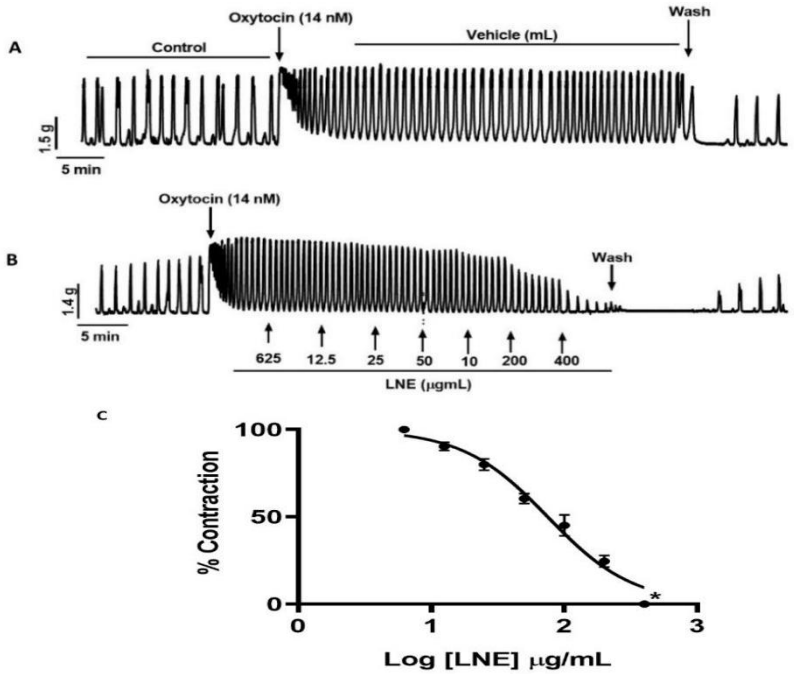


Figure 2. Effect of LNE on uterine contractions induced by oxytocin (14 nM) in non-pregnant mice. Recordings of (A) the response of uterine tissue to oxytocin, and (B) the effect of LNE (6.25 – 400 µg/mL) on uterine contractions induced with oxytocin in non-pregnant mice. (C) Concentration-response curve showing the effect of LNE on contractions induced by oxytocin. Values are mean ± SEM, n = 5 animals. *P < 0.05 compared to oxytocin effect.

3.3 Effect of LNE on uterine contractions induced by high KCl

Depolarization with high KCl (80 mM) induced rapid and sustained tonic contractions of uterine strips (Figure 3A). LNE (6.25 – 400 µg/mL) significantly inhibited KCl-induced contractions in a concentration-dependent manner. The inhibitory effect became significant at 25 µg/mL, with an IC_{50} value of 35.04 µg/mL.

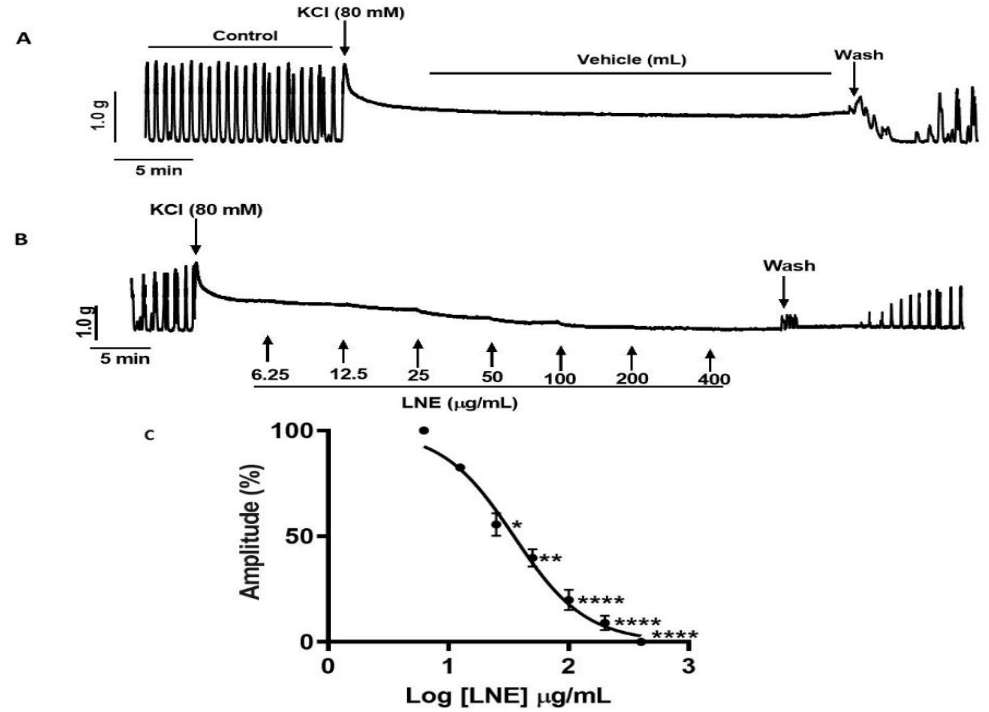
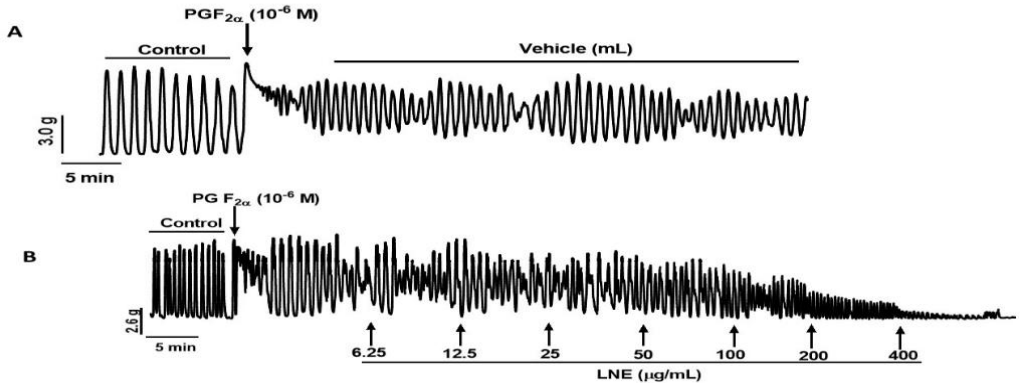


Figure 3. Effect of LNE on uterine contractions induced by high KCl (80 mM) in non-pregnant mice. Recordings of (A) the response of uterine tissue to high KCl, and (B) the effect of LNE (6.25-400 µg/mL) on uterine contractions induced with high KCl in non-pregnant mice. (C) Concentration-response curve showing the effect of LNE on contractions amplitude induced by high KCl. Values are mean ± SEM, n = 5 animals; *P < 0.05, **P < 0.01 and ****P < 0.0001 compared to high KCl effect.

3.4 Effect of LNE on uterine contractions induced by $PGF_{2}\alpha$

$PGF_{2}\alpha$ (10^{-6} M) produced strong uterine contractions characterized by increased contractile force. LNE (6.25 – 400 µg/mL) progressively inhibited $PGF_{2}\alpha$-induced contractions, with significant reduction observed at 200 µg/mL. The force integral decreased from 100% to 28.71%, with an IC_{50} value of 88.54 µg/mL.



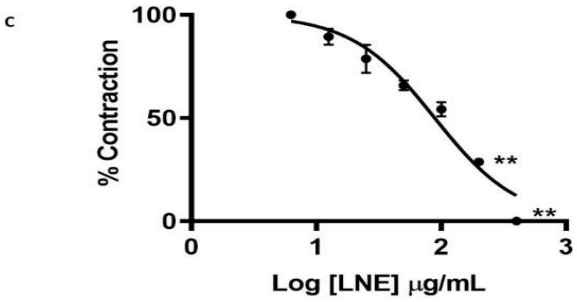


Figure 4. Effect of LNE on uterine contractions induced by prostaglandin $F_2\alpha$ ($PGF_2\alpha$, 10^{-6} M) in non-pregnant mice. Recordings of (A) the response of uterine tissue to $PGF_2\alpha$, and (B) the effect of LNE (6.25 – 400 µg/mL) on uterine contractions induced with $PGF_2\alpha$ in non-pregnant mice. (C) Concentration-response curve showing the inhibitory effect of LNE on contractions induced by $PGF_2\alpha$. Values are mean ± SEM, n = 4 animals. **P < 0.01 compared to $PGF_2\alpha$ effect.

3.5 Effect of LNE on uterine contractions induced by oxytocin in calcium-free medium

In calcium-free physiological solution containing EDTA, oxytocin induced phasic contractions mediated primarily by intracellular calcium release (Figure 5A). Addition of LNE (400 µg/mL) reduced the frequency of contractions; however, the reduction in contraction amplitude was not statistically significant (Figure 5B, 5C).

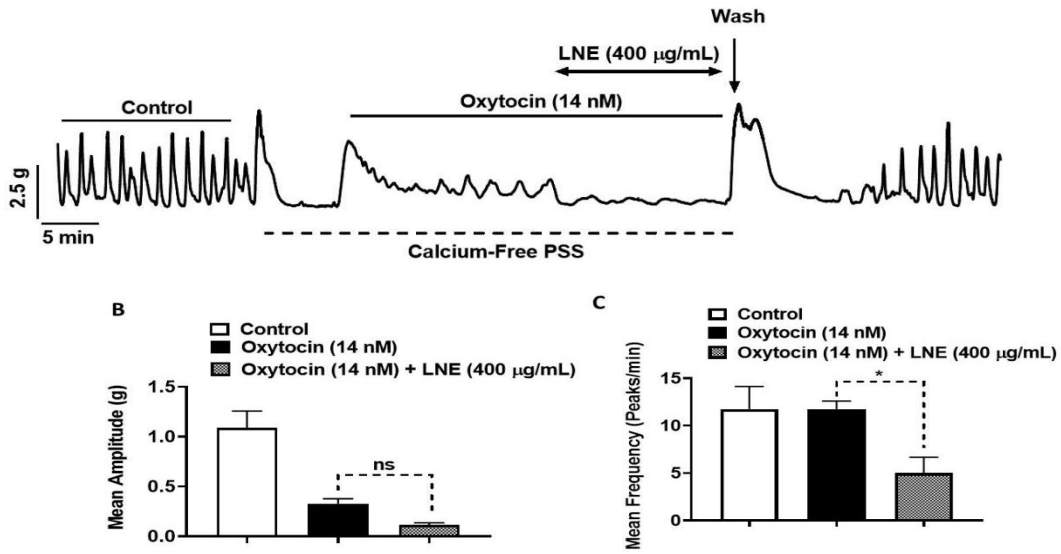


Figure 5. Effect of LNE on uterine contractions induced by oxytocin (14 nM) in calcium-free medium in non-pregnant mice. (A) Recording of the response of uterine tissue to oxytocin in calcium-free medium and effect of LNE on oxytocin-induced contractions in non-pregnant mice, (B) and (C). the inhibitory effect of LNE on contractions amplitude, and frequency induced by oxytocin. Values are mean ± SEM, n = 4 animals. *P < 0.05 compared to oxytocin effect.

3.6 Effect of LNE on uterine contractions induced by MCh

MCh (10 µM) increased the amplitude and frequency of uterine contractions compared with spontaneous contractions (Figure 6A). Cumulative addition of LNE progressively inhibited MCh-induced contractile activity (Figure 6B), with significant inhibition observed from 50 µg/mL (Figure 6C). The calculated IC_{50} value was 65.74 µg/mL.

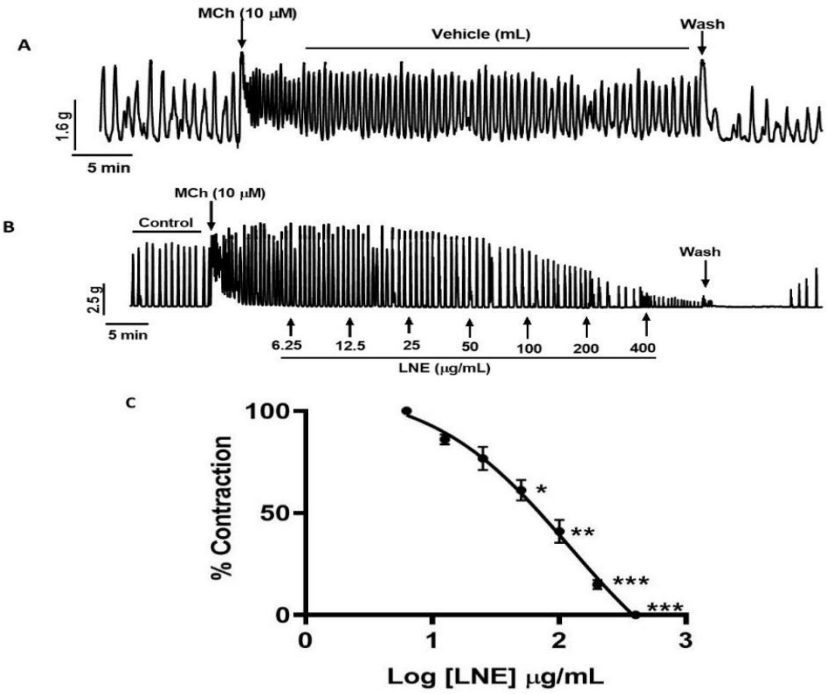
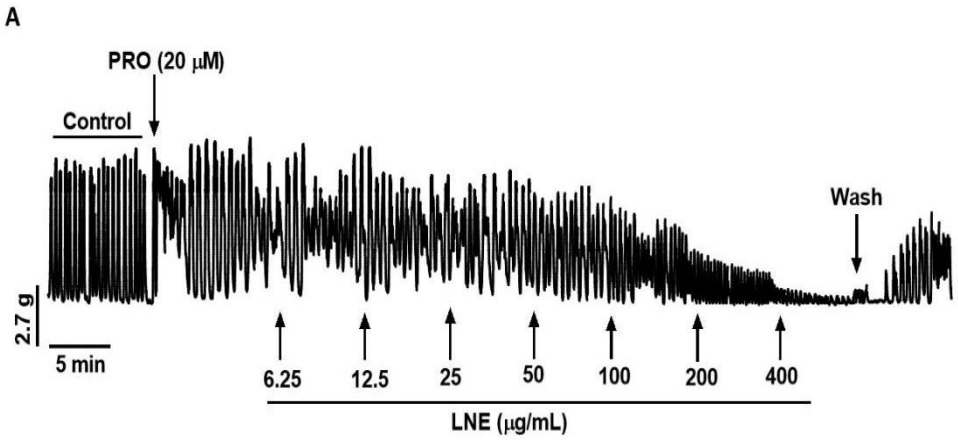


Figure 6. Effect of LNE on uterine contractions induced by methacholine (MCh, 10 μM) in non-pregnant mice. Recordings of (A) the response of uterine tissue to MCh, and (B) the effect of LNE (6.25 – 400 μg/mL) on uterine contractions induced with MCh in non-pregnant mice. (C) Concentration-response curve showing the inhibitory effect of LNE on contractions induced by MCh. Values are mean ± SEM, n = 4 animals. *P < 0.05, **P < 0.01, and ***P < 0.001 compared to methacholine effect.

3.7 Role of β-Adrenergic Receptors and Potassium Channels

Pretreatment with propranolol (20 μM) or TEA (5 mM) did not significantly modify the inhibitory effects of LNE on uterine contractions (Figure 7A and 8B respectively). The IC_{50} values obtained in the presence of propranolol (63.14 μg/mL) and TEA (53.82 μg/mL) were comparable to that observed with LNE alone (69.07 μg/mL) (Figure 7B and 8C respectively).



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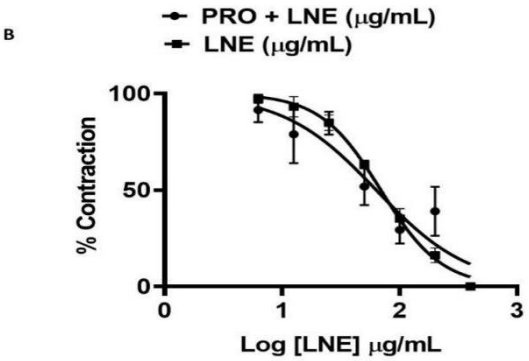

Figure 7. Effect of LNE on uterine contractions in the presence of propranolol (PRO, 20 μM) in non-pregnant mice. (A) Recording of the effect of LNE (6.25 – 400 μg/mL) on uterine contractions in the presence of propranolol. (C) Concentration-response curves showing the effect of LNE on uterine contractions in non-pregnant mice in the presence and absence of propranolol. Values are expressed as mean ± SEM; n = 4 animals.

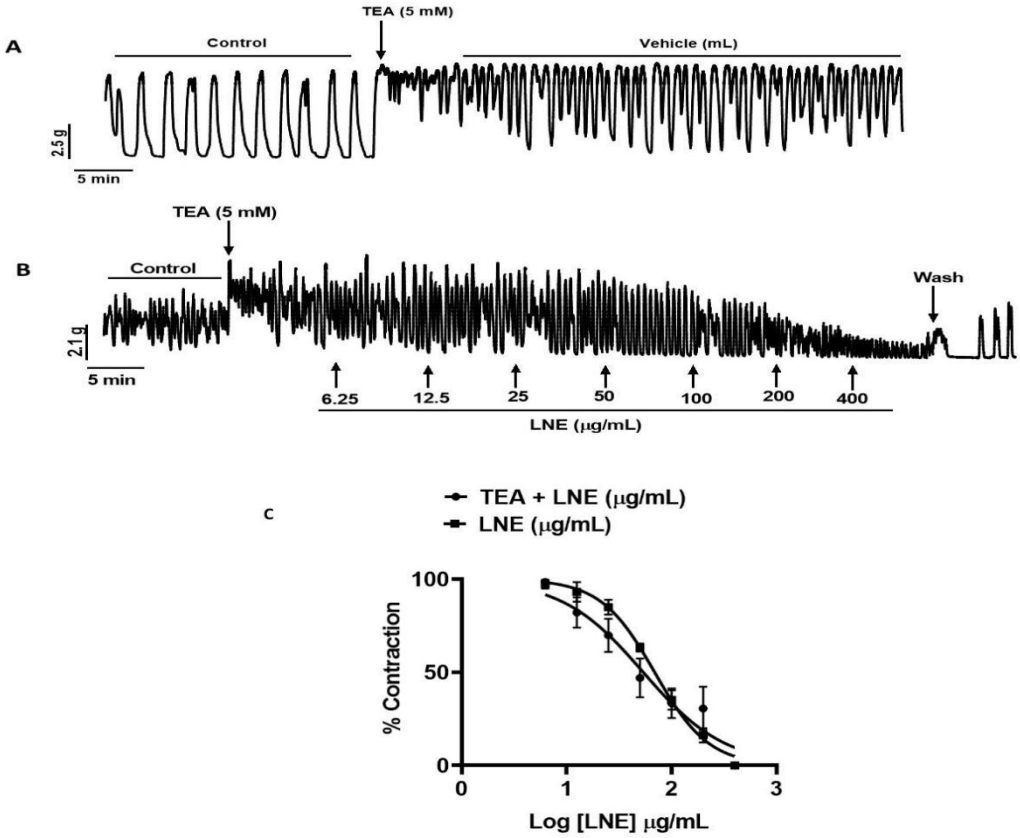

Figure 8. Effect of LNE on uterine contractions in the presence of tetraethylammonium (TEA, 5 mM) in non-pregnant mice. Recordings of (A) the response of uterine strip to TEA, and (B) the effect of LNE (6.25 – 400 μg/mL) on uterine contractions in the presence of TEA. (C) Concentration-response curves showing the effect of LNE on uterine contractions in non-pregnant mice in the presence and absence of TEA. Values are expressed as mean ± SEM; n = 4 animals.

4. DISCUSSION

The present study demonstrates that LNE produces significant inhibitory effects on uterine contractility. LNE suppressed spontaneous uterine activity and contractions induced by oxytocin, $PGF_2\alpha$, MCh, and membrane depolarization with high KCl. These observations suggest that *L. nobilis* possesses marked uterine relaxant (tocolytic) activity and may partly explain its traditional use in the management of dysmenorrhoea. Spontaneous uterine contractions are a characteristic property of myometrial tissue and arise from intrinsic pacemaker activity involving periodic changes in intracellular calcium levels and membrane excitability [18, 19]. In this study, LNE markedly reduced contraction amplitude and overall contractile activity without significantly altering contraction

frequency. This suggests that the extract primarily reduces the force of myometrial contraction rather than the rate of pacemaker activity. This pattern indicates that LNE may act by interfering with the contractile machinery or calcium availability required for force generation. The rapid recovery of contractions after washing further indicates that the effect of the extract is reversible and likely pharmacological rather than cytotoxic. Oxytocin is a well-known uterotonic hormone that stimulates uterine contractions by activating oxytocin receptors coupled to phospholipase C signaling pathways, leading to increased intracellular calcium release and enhanced calcium influx through voltage-dependent calcium channels [20]. Oxytocin and prostaglandins (particularly $PGF_2\alpha$) are major mediators of uterine contractility and play key roles in the pathophysiology of dysmenorrhoea [20, 21, 22]. The ability of LNE to attenuate oxytocin- and $PGF_2\alpha$-induced contractions indicates that the extract may interfere with calcium-dependent signaling pathways involved in uterine smooth muscle contraction. This finding is particularly relevant because pharmacological agents used in the treatment of dysmenorrhoea, such as non-steroidal anti-inflammatory drugs (NSAIDs), exert their therapeutic effect primarily by reducing prostaglandin production or action [23]. Therefore, the ability of LNE to attenuate prostaglandin-induced contractions provides experimental support for its potential use in the management of menstrual pain. Additional insight into the mechanism underlying the uterine relaxant activity of LNE was obtained using high KCl (80 mM). High extracellular K^+ causes membrane depolarization, which leads to the opening of voltage-dependent calcium channels and subsequent influx of extracellular calcium, resulting in sustained smooth muscle contraction [17, 24]. In this study, LNE potently inhibited KCl-induced contractions in a concentration-dependent manner, with a relatively low IC_{50} value. This observation strongly suggests that the extract may interfere with calcium entry through voltage-dependent calcium channels. This mechanism is consistent with previous reports describing calcium channel inhibitory effects of *L. nobilis* extract in vascular smooth muscle [13]. Experiments performed in calcium-free medium revealed only modest inhibition of oxytocin-induced contractions, suggesting that the extract exerts limited influence on intracellular calcium release. MCh, a non-selective muscarinic receptor agonist, stimulates uterine contractions primarily through activation of M_3 receptors, leading to increased intracellular calcium through phospholipase C signaling [25]. In this study, MCh markedly increased uterine contractile activity, which was progressively inhibited by LNE. This inhibitory effect suggests that LNE may interfere with muscarinic receptor-mediated signaling or downstream calcium-dependent contractile mechanisms. Since muscarinic receptor activation ultimately increases the intracellular calcium availability, the ability of LNE to suppress MCh-induced contractions further supports the hypothesis that the extract reduces uterine contractility by limiting calcium availability required for smooth muscle contraction. To further elucidate the possible mechanisms responsible for the inhibitory effects of LNE, the involvement of β-adrenergic receptors and potassium channels was investigated using propranolol and TEA, respectively. Activation of β_2-adrenergic receptors typically produces uterine relaxation through increased cyclic AMP levels [26], while opening of potassium channels leads to membrane hyperpolarization and reduced calcium influx [27]. In the present study, pretreatment with propranolol or TEA did not prevent the inhibitory effects of LNE on uterine contractions. These findings indicate that the relaxant effect of LNE is unlikely to be mediated through β-adrenergic receptor activation or potassium channel opening. The pharmacological effects observed in this study may be attributed to the diverse phytochemical constituents present in *L. nobilis* leaves. Previous phytochemical analyses have identified compounds such as 1,8-cineole, eugenol, linalool, and various flavonoids, many of which have been reported to possess smooth muscle relaxant, anti-inflammatory properties and ability to modulate calcium channels activity [28, 29, 30]. Therefore, the inhibitory effects of LNE on uterine contractility may result from the synergistic actions of these bioactive constituents. Overall, the results of the present study clearly provide experimental evidence that LNE exerts significant inhibitory effects on uterine smooth muscle contractility. The findings indicate that the extract reduces uterine contractions primarily by limiting extracellular calcium influx, with minimal involvement of β-adrenergic receptors or potassium channels. The ability of LNE to suppress contractions induced by oxytocin, prostaglandins, MCh, and membrane depolarization supports its potential pharmacological relevance in the management of dysmenorrhoea and other conditions associated with excessive uterine contractility. However, certain limitations should be acknowledged. The present study used crude plant extract and did not isolate the specific active compounds responsible for the observed effects. Further studies are required to identify the active constituents and to evaluate their pharmacological effects *in vivo.*

5. CONCLUSION

This study has provided the first evidence that LNE produces relaxant effects in the non-pregnant mouse uterus. The possible underlying mechanisms of LNE-induced relaxant effect are likely mediated through blockade of extracellular calcium influx via L-type calcium channels and inhibition of calcium release from intracellular stores.

Acknowledgment
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Conflicts of Interest
The authors declare no conflict of interest

Contribution of the authors
Adaeze P. Uchendu: Conceptualization, Methodology, Investigation, Resources, Supervision, Data Analysis, Visualization, Manuscript review and editing. Miracle U. Nwachukwu: Methodology, Investigation, Manuscript drafting

Ethical approval
All procedures were approved by the Faculty of Pharmacy Ethics Committee, University of Benin, Nigeria (EC/FP/026/035).
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