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Spasmolytic activity of *Myristica fragrans* Houtt. ethanol seed extract and its fractions on isolated murine uterus: possible involvement of calcium-dependent pathways

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Abstract
Myristica fragrans Houtt. (nutmeg) is widely used in traditional medicine for the treatment of gastrointestinal spasms and other smooth muscle disorders. However, its direct effects on uterine smooth muscle contractility remain poorly understood. This study investigated the effects of the ethanol seed extract *of M. fragrans* (MFSE) and its fractions on spontaneous and agonist-induced uterine contractions in isolated murine uterus. Uterine strips obtained from non-pregnant female Swiss mice were mounted in an organ bath containing physiological saline solution, and isometric contractions were recorded. The effects of cumulative concentrations of MFSE and its fractions were evaluated on spontaneous, oxytocin-induced, high potassium (KCl)-induced, and oxytocin-induced contractions in calcium-free medium. MFSE and its fractions produced significant, concentration-dependent inhibition of spontaneous uterine contractions, reducing contraction amplitude, frequency, and area under the curve ($P < 0.05$). Similar inhibitory effects were observed against oxytocin- and KCl-induced contractions. The dichloromethane fraction exhibited the greatest inhibitory potency, particularly against KCl-induced contractions (IC_{50} = 0.0048 ± 0.004 mg/mL), while the crude extract demonstrated broad inhibitory activity. In calcium-free medium, MFSE and its fractions also suppressed oxytocin-induced transient contractions. These findings indicate that *M. fragrans* possesses significant uterine relaxant activity, possibly mediated through modulation of calcium-dependent pathways.

Keywords: Calcium-channel blockade*; Myristica fragrans*; Nutmeg; Spasmolytic activity; Uterine contractility

INTRODUCTION

Uterine contractility is essential for normal reproductive processes, including menstruation, sperm transport, implantation, and parturition [1]. The rhythmic contractions and relaxation of the myometrium are regulated by a complex interplay of hormonal, biochemical, and electrophysiological mechanisms [2], and disturbances in this regulation contribute to disorders such as dysmenorrhoea, preterm labour, and other uterine motility disorders [3, 4]. Consequently, the identification of agents capable of modulating uterine smooth muscle activity remains an important area of research in reproductive pharmacology.

Myometrial contraction is largely dependent on intracellular calcium ($[Ca^{2+}]_i$)

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dynamics [5, 6]. Calcium influx through voltage-gated calcium channels (VGCCs), together with calcium release from intracellular stores via inositol triphosphate (IP_3)-mediated pathways, initiates and sustains uterine contractions [3, 5, 6]. Agonists such as oxytocin stimulate uterine contractions by activating G protein-coupled receptors, leading to phospholipase C activation, IP_3 generation, and subsequent calcium mobilization [7, 8]. Similarly, high extracellular potassium (KCl) depolarizes the myometrial membrane and promotes calcium entry through VGCCs, resulting in sustained tonic contractions [9, 10]. Thus, compounds capable of interfering with calcium-dependent signalling pathways may possess therapeutic potential as uterine relaxants or stimulants. Several drugs are currently used to suppress uterine contractions or relieve uterine spasms. Calcium channel blockers such as nifedipine are widely employed as tocolytic agents because they reduce calcium ion (Ca^{2+}) influx into myometrial cells. Oxytocin receptor antagonists, including atosiban, inhibit oxytocin-mediated uterine contractions, while β_2-adrenoceptor agonists such as terbutaline and ritodrine promote uterine relaxation through increased cyclic adenosine monophosphate (cAMP) production. In addition, non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the management of primary dysmenorrhoea through the inhibition of prostaglandin synthesis [11, 12]. Despite their clinical usefulness, these agents are associated with limitations including maternal hypotension, tachycardia, pulmonary oedema, foetal cardiovascular effects, contraindications and variable efficacy [13, 14]. These shortcomings have stimulated continued interest in identifying safer and more affordable uterine relaxants from medicinal plants.

Medicinal plants continue to represent an important source of bioactive compounds with therapeutic potential against smooth muscle disorders [15]. *Myristica fragrans* Houtt. (family Myristicaceae) is an evergreen tree native to Indonesia, and widely used both as a culinary spice and as a medicinal plant [16, 17].

Phytochemical studies have shown that *M. fragrans* seeds contain lignans, neolignans, flavonoids, terpenoids, phenolic compounds, alkaloids and essential oils [18], many of which possess antioxidant, anti-inflammatory, antimicrobial, antidiabetic, and potential anticancer activities, with reported therapeutic benefits in neurological, digestive, and cardiovascular disorders [19, 20, 21]. Previous studies have showed that *M. fragrans* inhibits prostaglandin synthesis and suppresses smooth muscle contractions in gastrointestinal tissues while demonstrating antispasmodic activity in isolated guinea pig ileum preparations [22, 23]. Toxicological studies have also shown that ethanol seed extract of *M. fragrans* possesses a favourable safety profile following acute and subacute administration in female rats [24].

Although several medicinal plants have been investigated for uterine relaxant activity, information on the effects of *M. fragrans* on myometrial contractility remains scarce. Moreover, comparative evaluation of its solvent fractions has not been reported. Therefore, this study investigated the effects of the ethanol seed extract of *M. fragrans* and its fractions on spontaneous, oxytocin-induced, and KCl-induced contractions in isolated murine uterus. These findings may provide mechanistic insights into its modulatory effects on uterine smooth muscle and support its potential application in the management of uterine contractile disorders.

EXPERIMENTAL METHODS

Drugs, chemicals and reagents. Oxytocin injection (10 IU/mL) was obtained from Anhui Hongye Pharmaceutical Co., Ltd. (China). Ethanol, dichloromethane, ethyl acetate and n-hexane were sourced from Fharmatrends, Nigeria. Ethylenediaminetetraacetic acid

disodium salt (EDTA) (Kermel, China). The physiological salt solution (PSS) was prepared using analytical-grade reagents including sodium chloride (NaCl; Honeywell Fluka, Germany), sodium bicarbonate ($NaHCO_3$; Sigma-Aldrich, USA), D-glucose (Sigma-Aldrich, USA), potassium chloride (KCl; Guangdong Guanghua Sci-Tech, China), and calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$; Kermel, China). PSS was freshly prepared before each experiment.

Plant material collection and identification. Dried seeds of *M. fragrans* were procured from Oba Market, Oredo Local Government Area, Benin City, Edo State, Nigeria, in July 2025. Botanical authentication was carried out by Professor Henry Akinnibosun Adewale, a plant taxonomist, of Department of Plant Biology and Biotechnology, University of Benin, Benin City, Nigeria. A voucher specimen (UBH-M537) was deposited in the Departmental Herbarium for future reference.

Extraction and fractionation procedure. The seeds were cleaned, air-dried, and pulverized into fine powder using an electric grinder. Approximately 400 g of the powdered seed material was extracted with 2.5 L of ethanol using a Soxhlet apparatus. The solvent was subsequently removed under reduced pressure using a rotary evaporator, and the residue was further dried at 40ºC to obtain the *M. fragrans* ethanol extract (MFSE). A total of 93.6 g of MFSE was dissolved in 200 mL distilled water, transferred into a separating funnel, equilibrated, and successively partitioned with 200 mL of n-hexane, dichloromethane and ethyl acetate until clear fractions of increasing polarity were obtained. The resulting fractions of *M. fragrans* (n-hexane fraction, NHMF; dichloromethane fraction, DCMF; ethyl acetate fraction, EAMF) were concentrated using a rotary evaporator, and then, oven-dried at 40°C. The dried extract and fractions were kept at 4°C until further experiments.

Experimental animals. Female Swiss mice (22–28 g, aged 7–9 weeks) were obtained from the Animal House of the Department of Pharmacology and Toxicology, University of Benin. Animals were housed under standard laboratory conditions at 24 ± 2°C under a 12-hour light/12-hour dark cycle, with free access to food (Chikun grower pellets Feeds, Crown flour mill Limited, Lagos, Nigeria), and clean drinking water. All experimental procedures complied with institutional ethical guidelines and were approved by the Faculty Ethics Committee (Approval No. EC/FP/024/13).

Preparation of uterine tissue and evaluation of contractility. Only non-pregnant mice confirmed to be in oestrus phase through cytological evaluation of vaginal smears, were euthanised by cervical dislocation. The uterine horns were immediately excised and placed in a dissecting dish containing prewarmed (37ºC), oxygenated PSS with the following composition (in mM/L NaCl - 154.00, $NaHCO_3$ - 5.95, d-glucose - 2.78, KCl - 5.63, and $CaCl_2 \cdot 2H_2O$ - 2.05. The uterine horns, carefully cleaned of adherent connective tissues, were cut into segments (approx. 2 mm) and mounted longitudinally in a 10 mL organ bath containing the same oxygenated (100% O_2) PSS, maintained at 37ºC. Changes in isometric contractions were recorded using a Panlab system (Panlab ADInstrument, Spain) connected to a bridge amplifier and a PowerLab data acquisition unit (PowerLab 2/26 Model ML825, ADInstruments, Australia) equipped with LabChart software (ADInstruments). The mounted tissue was subjected to a resting tension of 0.5 g, and a 40-minute equilibration period was allowed to obtain stable contractions [25].

Assessment of MFSE and its fractions on spontaneous uterine contractions. After spontaneous contractions were allowed to equilibrate, the rhythmic uterine contractions were observed and recorded for 10 minutes to establish baseline contractility. Increasing concentrations of MFSE (0.003 – 0.7 mg/mL)

were then added cumulatively at 5-minute intervals without washing. Changes in contraction amplitude and frequency were recorded. Following the final concentration, tissues were washed and allowed to recover. The same protocol was repeated for each fraction (EAMF, DCMF and N-HMF).

Assessment of MFSE and its fractions on agonist-induced contractions. To evaluate effects on stimulated contractions, uterine tissues were precontracted using oxytocin (11.62 nM), or potassium chloride (80 mM). Each agonist was allowed a contact time of 5 min to induce contractions. Without washing, cumulative concentrations of MFSE or its fractions (0.003 - 0.7 mg/mL) were added at 5 min intervals. Contractile responses were continuously recorded. Control experiments were conducted using the vehicle (distilled water).

Assessment of MFSE and its fractions on oxytocin-induced contractions in calcium-free medium. To investigate the involvement of intracellular calcium release, tissues were exposed to calcium-free PSS containing EDTA (0.1 mM). After stabilization, oxytocin (11.62 nM) was added to evoke contractions dependent on intracellular calcium release. Subsequently, MFSE or its fractions (0.3 mg/mL) was introduced, and changes in contractile activity were recorded.

Data analysis. Results are expressed as mean ± standard error of mean (SEM), n represents the number of animals used. Statistical comparisons were performed using the one-way analysis of variance (ANOVA) followed by Dunnett's *post hoc* multiple comparison test with $p < 0.05$, considered statistically significant. Contractile parameters (amplitude, frequency, and area under the curve [AUC]) were analysed using concentration-response curves fitted by nonlinear regression, based on a four-parameter logistic model according to the equation:

$$Y = \text{bottom} + (\text{top-bottom})/(1+10\hat{}((\log IC50-X) \times \text{hillslope})$$

where Y represents the response, X is the logarithm of MFSE or its fraction concentration, IC_{50} is the concentration producing 50% inhibition. GraphPad Prism version 8.01 (GraphPad Software Inc. San Diego, CA, USA) was used for all analyses.

RESULTS

Effect of MFSE and its fractions on Spontaneous Uterine Contractions. As shown in Figure 1A, cumulative administration of MFSE (0.003 – 0.7 mg/mL) produced a progressive reduction in spontaneous uterine contractility. Similar concentration-dependent inhibitory effects were observed with all fractions. Quantitative analysis showed that MFSE and all fractions significantly reduced contraction amplitude, frequency and area under the curve (AUC) compared with baseline spontaneous activity ($P < 0.05$) (Figure 1B – D). The inhibitory effects increased with increasing concentration for all treatments. The estimated IC_{50} values for amplitude, frequency and AUC are displayed in Table 1. MFSE produced IC_{50} values of 0.0263 ± 0.07 mg/mL, 0.0927 ± 0.11 mg/mL and 0.0169 ± 0.10 mg/mL for amplitude, frequency and AUC, respectively.

Effect of MFSE and fractions on oxytocin-induced uterine contractions. Application of oxytocin (11.62 nM) produced sustained rhythmic contractions characterized by increased amplitude and frequency compared with the vehicle-treated tissues (Figure 2A, a). Subsequent cumulative applications of MFSE and its fractions (0.003-0.7 mg/mL) produced a concentration-dependent inhibition of the oxytocin-induced contractions (Figure 2A, b-e). As shown in Figure 2B, MFSE and all fractions significantly reduced both contraction amplitude and frequency ($P < 0.05$) relative to oxytocin alone. DCMF exhibited the greatest inhibitory potency against oxytocin-induced contractions, with an IC_{50} value of

0.0280 ± 0.05 mg/mL for contraction amplitude. The corresponding IC_{50} values for MFSE, EAMF, and NHMF were 0.0460 ± 0.03 mg/mL, 0.0810 ± 0.07 mg/mL and 0.0736 ± 0.11 mg/mL, respectively (Table 2).

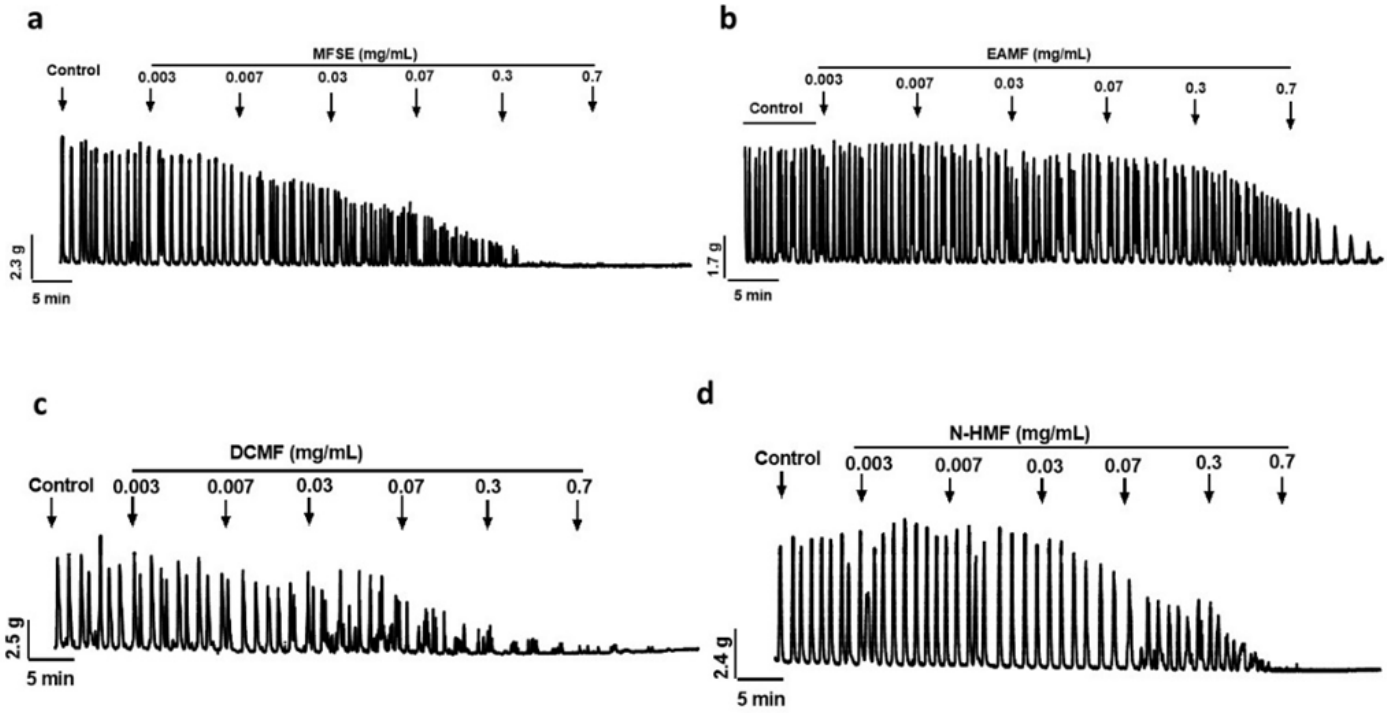

Figure 1A. Representative original tracings showing the inhibitory effect of MFSE (0.003 – 0.7 mg/mL) and fractions (0.003 – 0.7 mg/mL) on spontaneous contractions of isolated mouse uterus

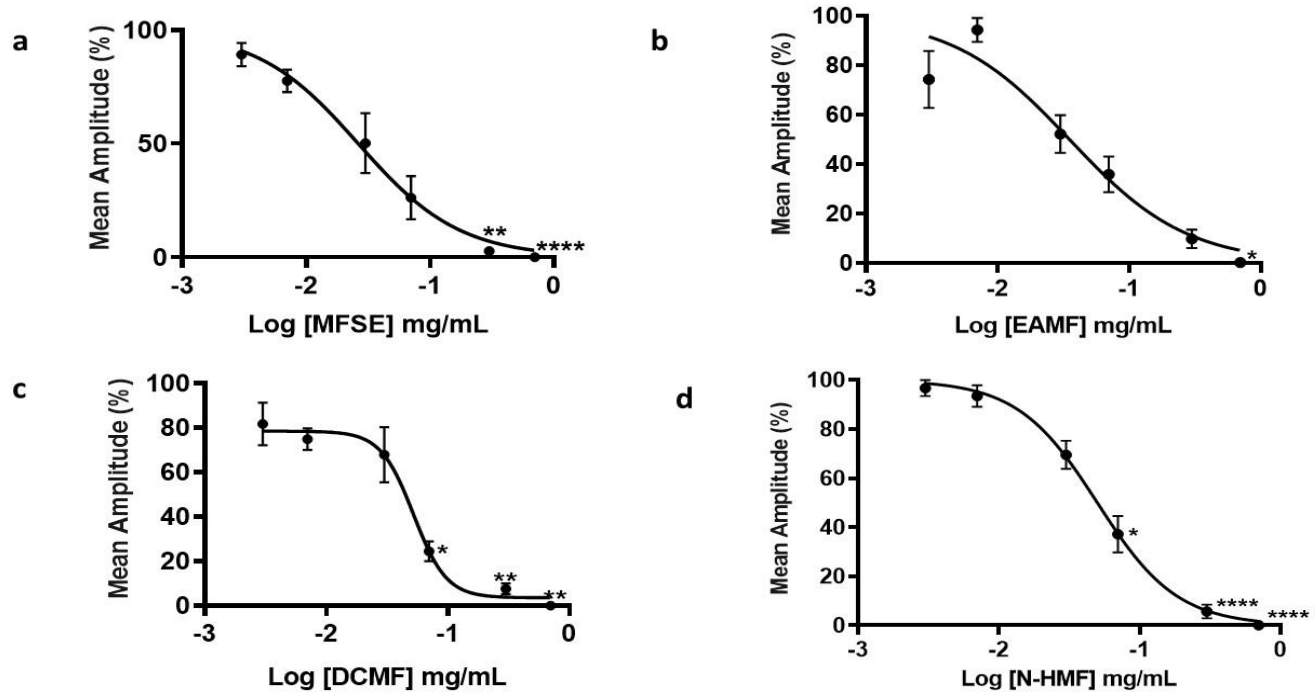

Figure 1B. Concentration-response curves showing effects MFSE (0.003 – 0.7 mg/mL) and fractions (0.003 – 0.7 mg/mL) on the spontaneous contraction amplitude. n = 5 animals, *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$

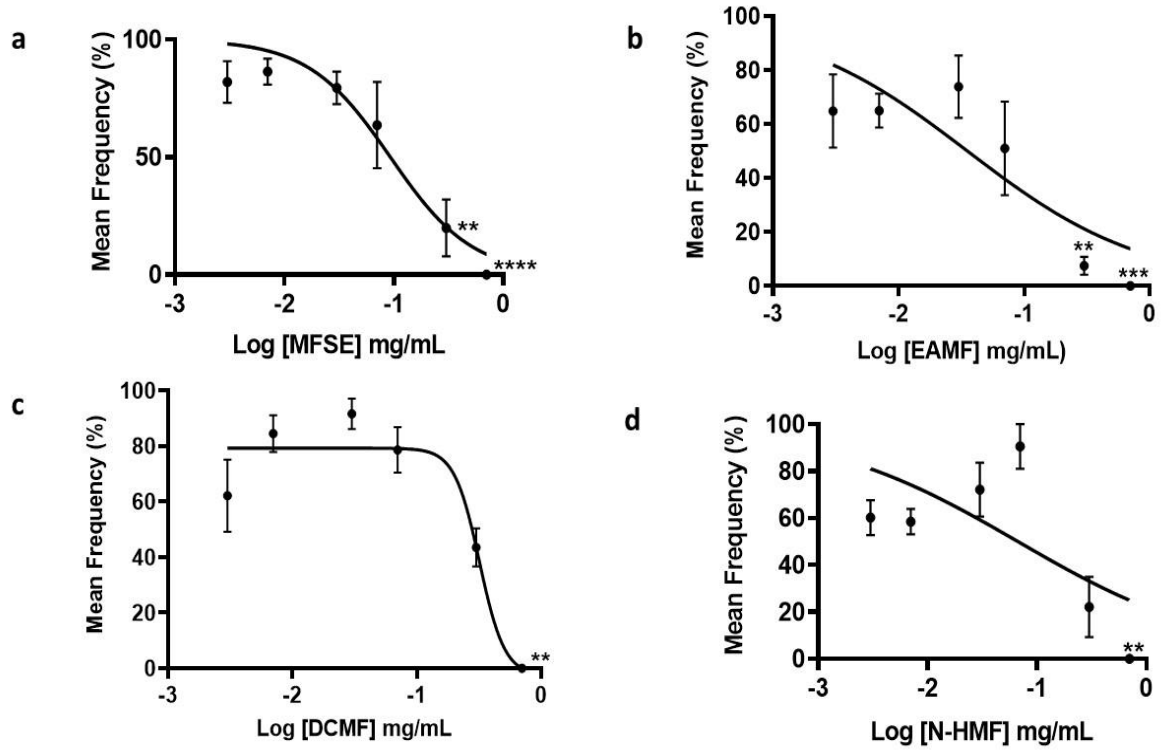

Figure 1C. Concentration-response curves showing effects of MFSE (0.003 – 0.7 mg/mL) and fractions (0.003 – 0.7 mg/mL) on the spontaneous contraction frequency. n = 5 animals, ***p<0.01, ***p<0.001, ****p<0.0001*

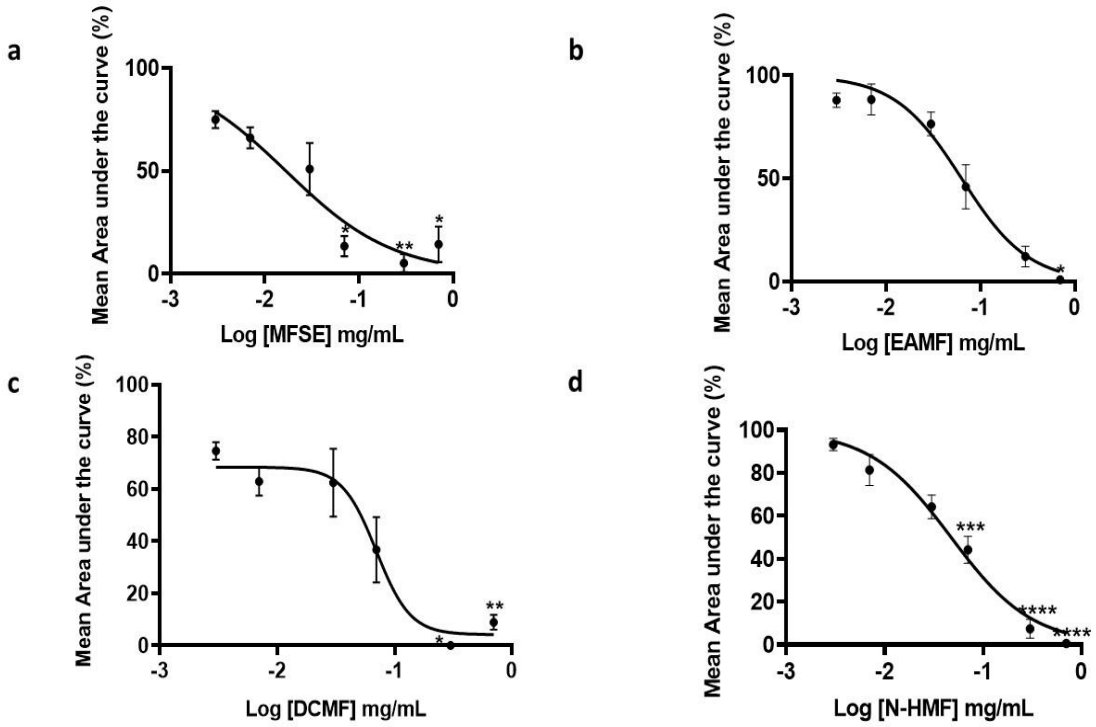

Figure 1D. Concentration-response curves showing effects MFSE (0.003 – 0.7 mg/mL) and fractions (0.003 – 0.7 mg/mL) on the spontaneous contraction area under the curve (AUC). n = 5 animals, **p <0.05, **p<0.01, ****p<0.0001*

Table 1: IC_{50} values (mg/mL) of MFSE and fractions on spontaneous uterine contractions

Parameter	MFSE	EAMF	DCMF	N-HMF
Amplitude (mg/mL)	0.0263 ± 0.07	0.0353 ± 0.09	0.0323 ± 0.09	0.0500 ± 0.04
Frequency (mg/mL)	0.0927 ± 0.11	0.0353 ± 0.18	0.1858 ± 0.11	0.0670 ± 0.25
AUC (mg/mL)	0.0169 ± 0.10	0.0636 ± 0.64	0.0250 ± 0.12	0.0474 ± 0.056

Effect of MFSE and fractions on high KCl-induced uterine contractions. Exposure of isolated uterine strips to 80 mM KCl produced sustained tonic contractions (Figure 3A). Treatment with MFSE and all fractions significantly diminished KCl-induced contractions in a concentration-dependent manner (Figure 3B). Among all treatments, the DCMF demonstrated the greatest inhibitory effect, with the lowest IC_{50} value (0.0048 ± 0.004 mg/mL), followed by N-HMF (0.0121 ± 0.05 mg/mL), EAMF (0.0278 ± 0.042 mg/mL), and MFSE (0.081 ± 0.06 mg/mL).

Effect of MFSE and fractions on oxytocin-induced uterine contractions in Ca2+-free medium. In calcium-free medium containing EDTA, oxytocin elicited transient uterine contractions (Figure 4A). Treatment with MFSE and all fractions significantly reduced both contraction amplitude and frequency compared with oxytocin-treated tissues ($P < 0.05$) (Figures 4B and 4C, a-d).

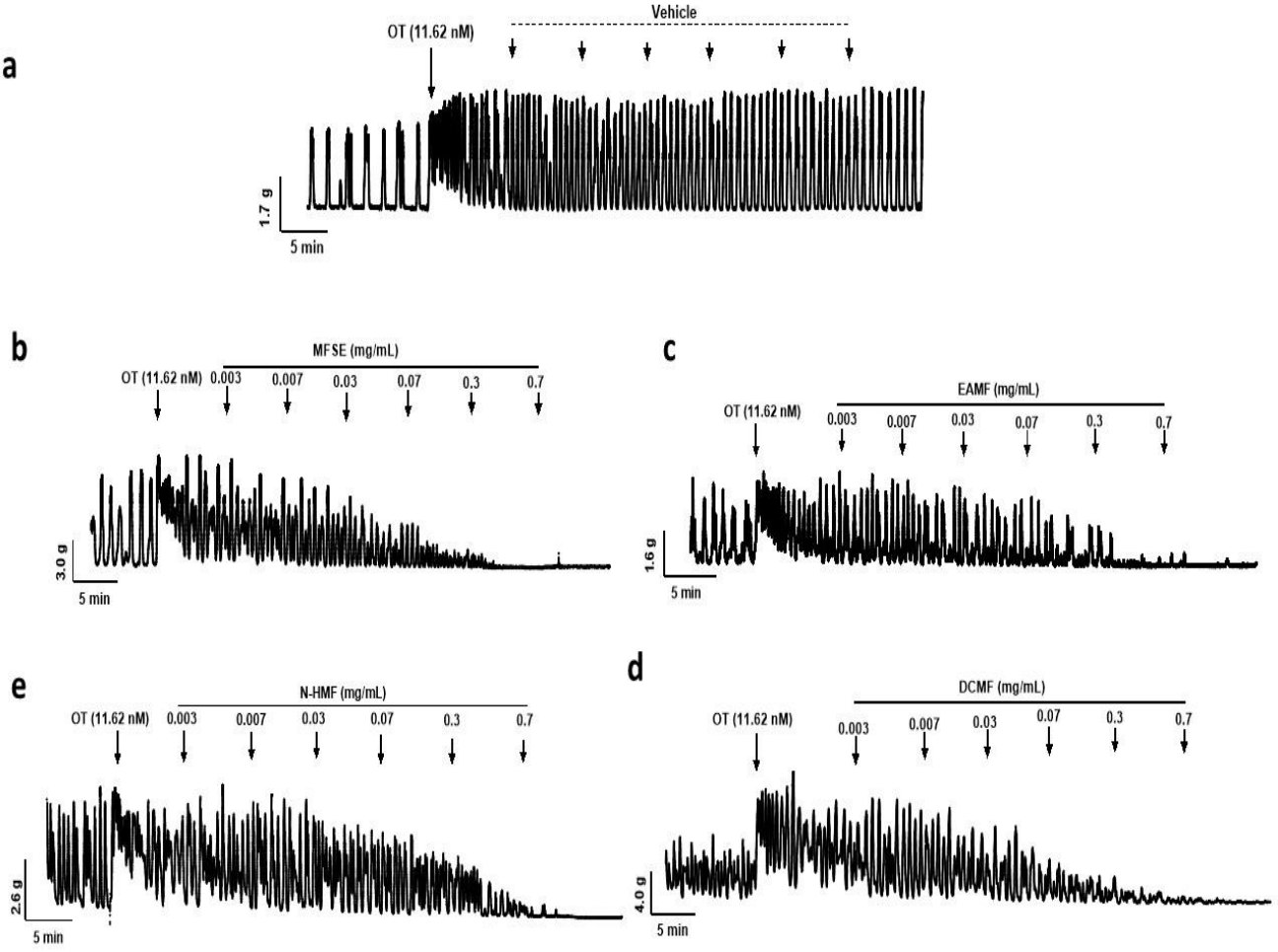

Figure 2A. Representative original tracings showing the inhibitory effect of MFSE (0.003 – 0.7 mg/mL) and fractions (0.003 – 0.7 mg/mL) on oxytocin-induced contractions

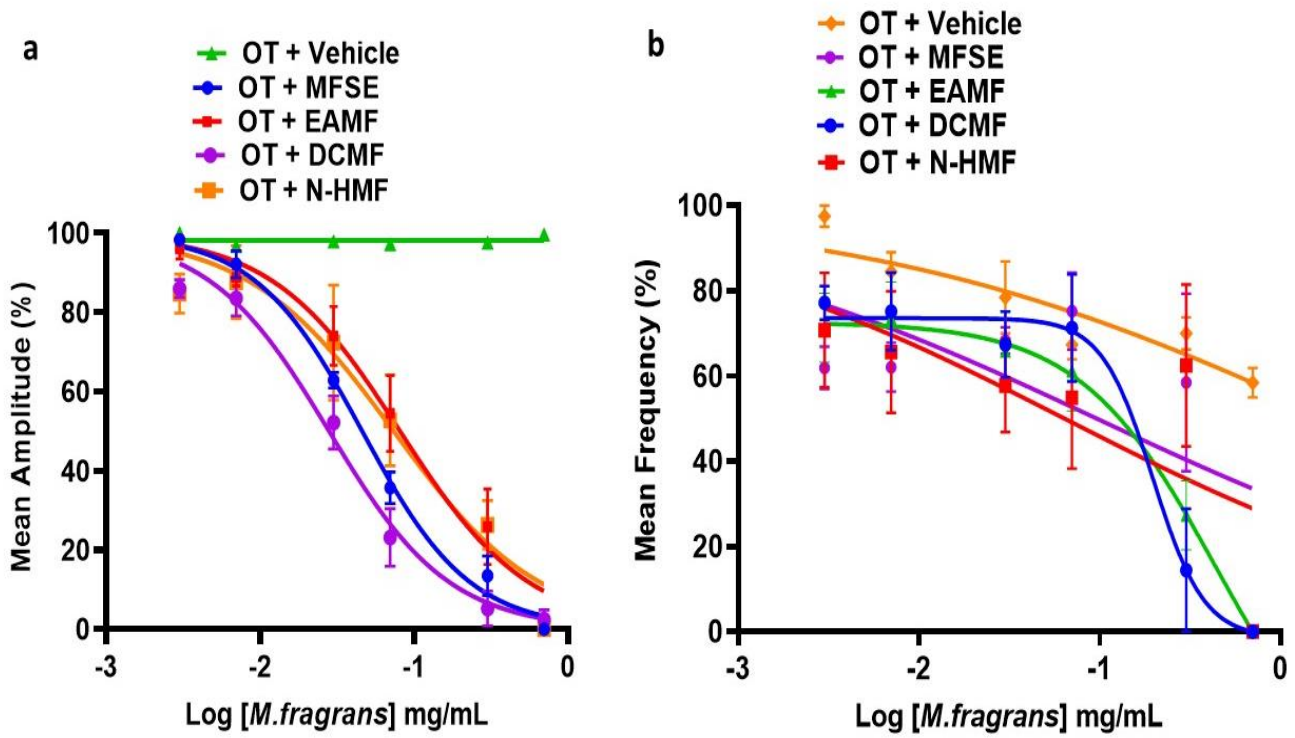

Figure 2B. Concentration-response curves showing the effects of MFSE and fractions on oxytocin-induced contraction amplitude (a) and frequency (b). n = 5 animals

Table 2: IC_{50} values (mg/mL) of MFSE and fractions on oxytocin-induced uterine contractions

Parameter	MFSE	EAMF	DCMF	N-HMF
Amplitude (mg/mL)	0.0460 ± 0.03	0.0810 ± 0.07	0.0280 ± 0.05	0.0736 ± 0.11
Frequency (mg/mL)	0.0962 ± 0.31	0.0567 ± 0.14	0.0693 ± 0.318	0.0638 ± 0.32

DISCUSSION

The present study demonstrates that MFSE and its fractions possess significant, concentration-dependent spasmolytic activity on isolated murine uterus. The extract and fractions inhibited spontaneous uterine contractions and significantly attenuated contractions induced by oxytocin and high potassium, indicating that *M. fragrans* contains bioactive constituents capable of reducing uterine smooth muscle contractility. These findings provide pharmacological support for the traditional use of *M. fragrans* in the management of spasmodic disorders.

MFSE and its fractions significantly reduced the amplitude, frequency and overall activity (AUC) of spontaneous uterine contractions. Since spontaneous myometrial activity depends largely on periodic membrane depolarization and extracellular calcium influx through VGCCs [9], the observed inhibition suggests interference with one or more calcium-dependent processes involved in maintaining basal uterine activity. Although all fractions were active, the EAMF showed stronger inhibition of contraction frequency, whereas the DCMF produced greater suppression of contraction amplitude. In contrast, the N-HMF displayed comparatively weaker effects. These differences likely reflect variations in the distribution of bioactive phytoconstituents according to solvent polarity.

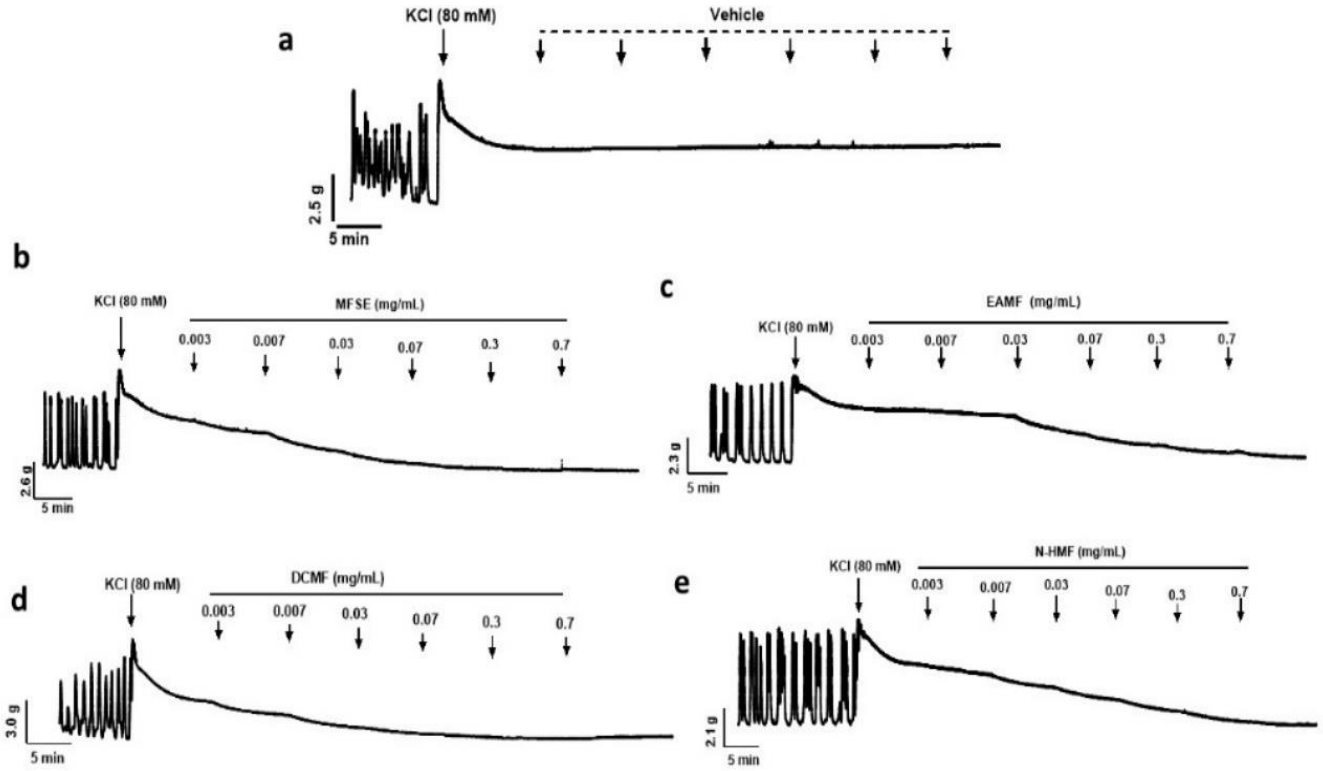

Figure 3A. Representative original tracings showing the inhibitory effect of MFSE (0.003 – 0.7 mg/mL) and fractions (0.003 – 0.7 mg/mL) on high KCl-induced contractions

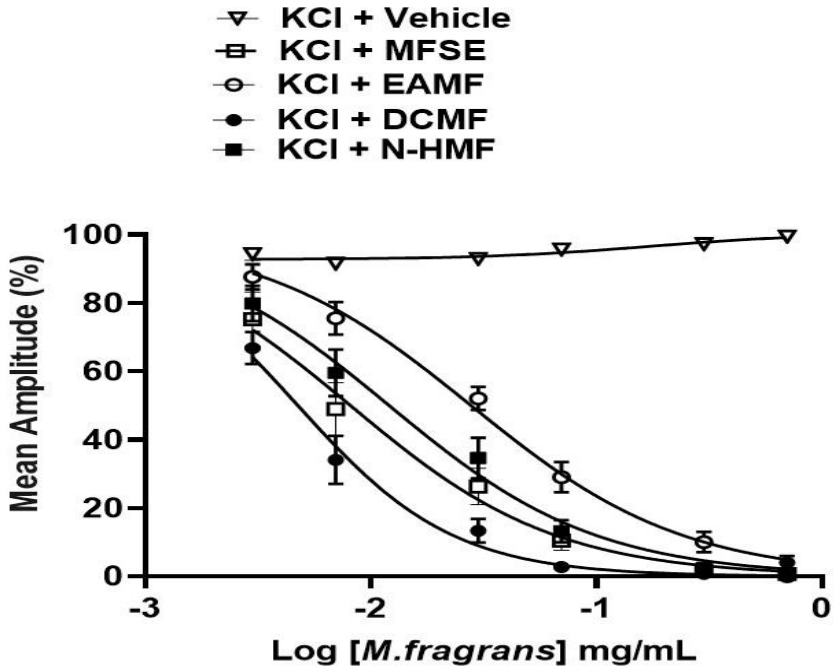

Figure 3B. Concentration-response curves showing the effects of MFSE and its fractions on high KCl-induced contraction amplitude. n = 5 animals

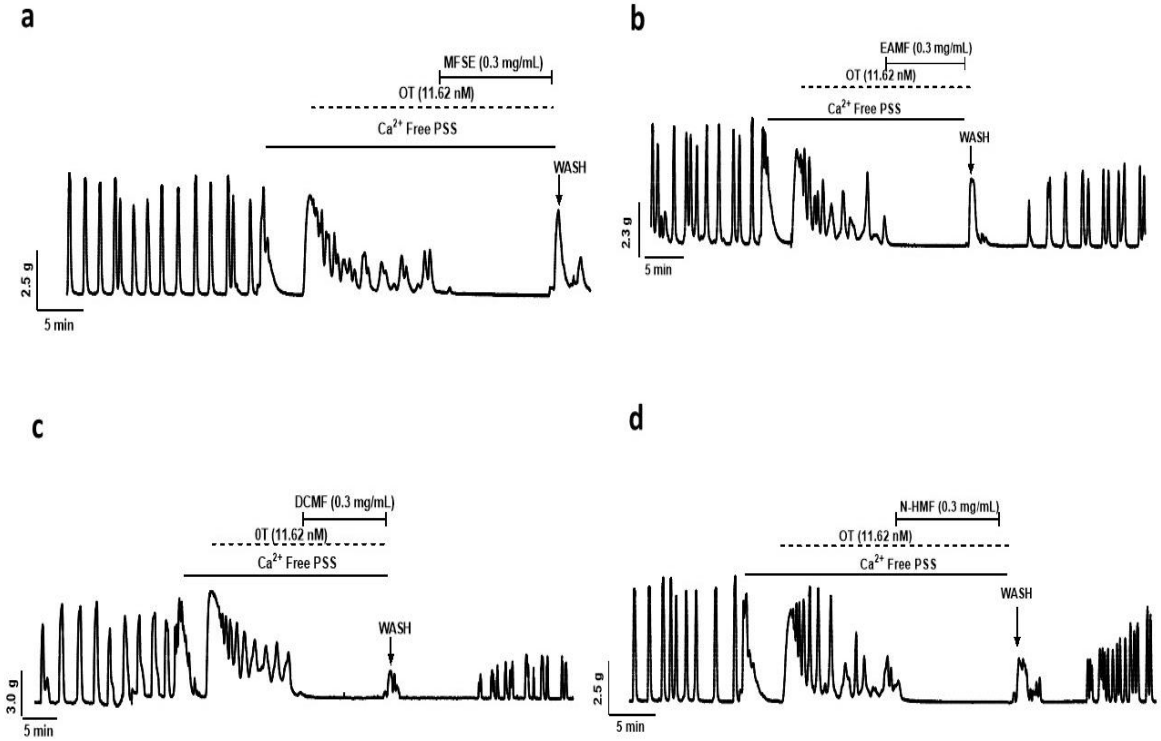

Figure 4A. Representative original tracings showing the inhibitory effect of MFSE (0.003 – 0.7 mg/mL) and fractions (0.003 – 0.7 mg/mL) on isolated mouse uterus pre-contracted with oxytocin (OT, 11.62 nM) in calcium free medium

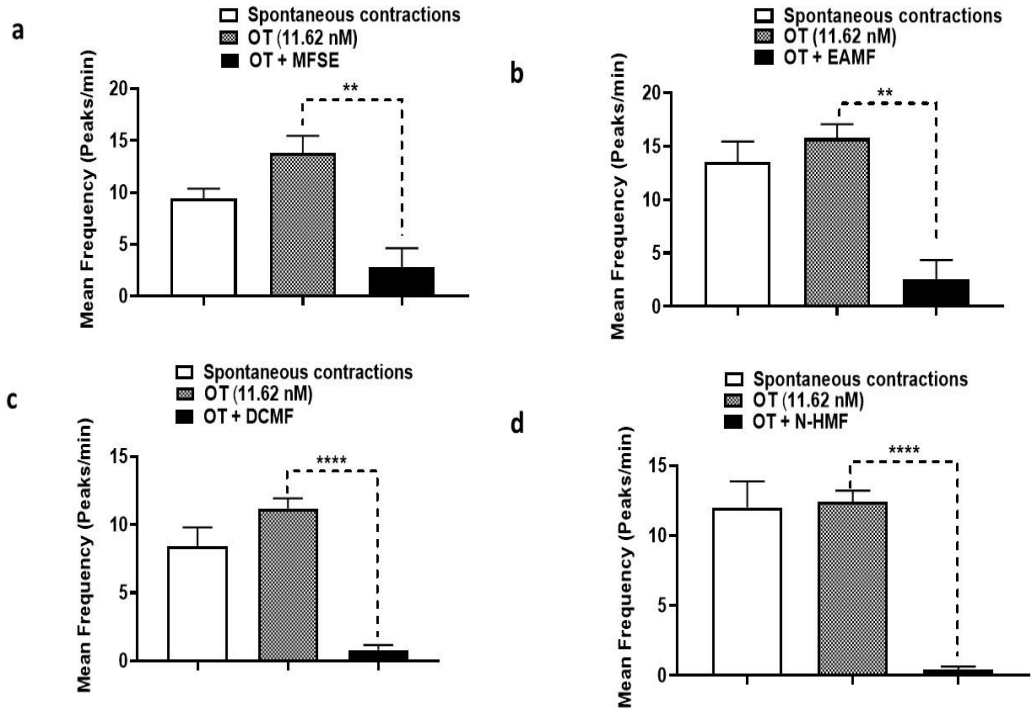

Figure 4B. Bar graphs showing the effects of MFSE (0.003 – 0.7 mg/mL) and fractions (0.003 – 0.7 mg/mL) on frequency of isolated mouse uterus pre-contracted with oxytocin (OT, 11.62 nM) in calcium free medium. n = 5 animals, **p<0.01, ****p<0.0001

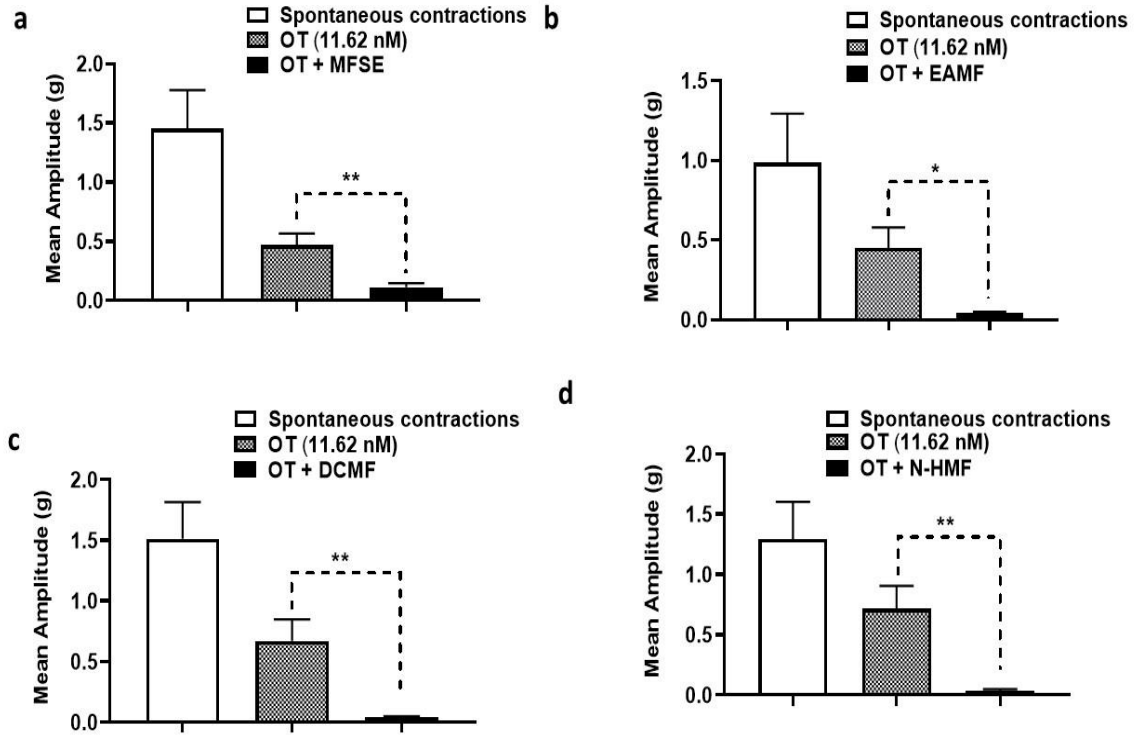

Figure 4C. Bar graphs showing the effects of MFSE (0.003 – 0.7 mg/mL) and fractions (0.003 – 0.7 mg/mL) on amplitude of isolated mouse uterus pre-contracted with oxytocin (OT, 11.62 nM) in calcium free medium. n = 5 animals, *p<0.05, **p<0.01

Oxytocin is a major physiological stimulant of uterine contraction. Binding of oxytocin to its Gq-coupled receptor activates phospholipase C (PLC), leading to the formation of inositol triphosphate (IP_3) and diacylglycerol, followed by mobilization of intracellular calcium and activation of the contractile apparatus [7]. In the present study, MFSE and its fractions significantly inhibited oxytocin-induced contraction, indicating that the extract interferes with receptor-mediated calcium mobilization and/or downstream signalling pathways. Among the fractions, DCMF exhibited the greatest inhibitory potency, indicating that moderately non-polar constituents may contribute substantially to the observed uterine relaxant activity. Although the crude extract demonstrated consistent activity, the enhanced potency of DCMF in some parameters suggests that fractionation may concentrate specific active constituents.

of smooth muscle by high extracellular potassium induces contraction primarily through activation of VGCC and subsequent calcium influx [26]. The significant inhibition of KCl-induced contractions by MFSE and its fractions, particularly DCMF, is therefore consistent with the possible involvement of calcium-dependent pathways. Similar observations have been reported for other medicinal plants with uterine relaxant activity, including *Pimpinella anisum*, in which inhibition of depolarization-induced contractions was associated with reduced calcium-dependent contractility [9].

In calcium-free PSS containing EDTA, oxytocin produced transient contractions attributed primarily to mobilization of intracellular calcium stores. MFSE and its fractions significantly reduced these transient responses. This indicates that the extract not only inhibits extracellular calcium influx but

may also interfere with intracellular calcium mobilization, possibly through modulation of IP_3-sensitive calcium stores.

An important strength of this study lies in the comparative evaluation of the crude extract and its fractions. While MFSE exhibited broad inhibitory activity across all experimental models, DCMF and EAMF frequently demonstrated greater potency in specific parameters. This suggests that fractionation not only separates phytochemicals based on polarity but also concentrates compounds with distinct pharmacodynamic properties. The superior activity of DCMF, particularly against KCl- and oxytocin-induced contractions, implies that moderately non-polar phytochemicals may play a dominant role in calcium channel blockade and receptor-mediated relaxation. Conversely, the relatively lower activity of N-HMF indicates that highly non-polar constituents alone may be insufficient for maximal uterine relaxation, or may require synergistic interactions with other phytochemicals present in the crude extract. However, because preliminary phytochemical screening and bioassay-guided fractionation was not undertaken, it is not possible to attribute the observed activity to specific phytochemical classes or individual compounds. Future studies should therefore focus on chromatographic isolation, structural characterisation and pharmacological evaluation of the active constituents within the dichloromethane fraction.

The present findings are consistent with previous reports describing the smooth muscle relaxant and antispasmodic activities of *M. fragrans* [23]. Ethanol seed extracts have been reported to inhibit gastrointestinal smooth muscle contractions, while the plant has also demonstrated anti-inflammatory, analgesic and antioxidant activities that may contribute indirectly to its traditional use in the management of spasmodic disorders [20, 21]. The present study extends previous observations by providing new evidence that the ethanol seed extract and its fractions possess uterine spasmolytic activity in the isolated murine uterus.

Conclusion. The findings of this study indicate that *M. fragrans* seed extract and its fractions exert significant, concentration-dependent uterine relaxant effects in isolated murine uterus, possibly through modulation of calcium-dependent pathways. The dichloromethane fraction showed the greatest inhibitory potency. These findings provide pharmacological support for the potential therapeutic usefulness in conditions associated with excessive uterine contractions. However, further studies to identify the active constituents and confirm their efficacy are required to establish their therapeutic potential.

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