ORIGINAL ARTICLE

ISSN: 0331 - 670X

https://doi.org/10.51412/psnnjp.2026.011

The Nigerian Journal of PHARMACY

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Modulatory Effects of Oxytocin-Specific Antagonist and Atropine on Uterine Contractions Induced by Methanol Extract of *Tacazzea apiculata In Vitro*

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ARTICLE INFO

Article history:

Received 08 March 2026
Revised 20 April 2026
Accepted 22 April 2026
Online Published

Keywords:

Tacazzea apiculata,
uterotonic activity,
oxytocin receptor,
uterine contraction,
albino rat

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ABSTRACT

Background: Uterotonic agents are vital in the management of labour, postpartum haemorrhage, and uterine dysfunction. Although *Tacazzea apiculata* is traditionally used for labour induction, its mechanism of action remains unknown. This study evaluated the mechanism underlying the uterotonic activity of the methanol stem extract of TA using isolated uterine strips from non-pregnant albino rats.

Methods: Estradiol-pretreated non-pregnant female rats (0.1 mg/kg, s.c.) were sacrificed by quick blow on the head, and uterine strips (~2 cm) were mounted in organ baths containing De Jalon's solution at 37°C and aerated with carbogen. Isometric contractions were recorded using a force transducer and PowerLab system. Concentration–response curves were generated for oxytocin (6.64×10^{-6}–53×10^{-5} mg/ml), acetylcholine (4×10^{-7}– 16×10^{-7} mg/ml), prostaglandin (2×10^{-6}– 16×10^{-6} mg/ml), and the extract (0.08–0.64 mg/ml). Tissues were pre-incubated with atosiban (4×10^{-5} mg/ml) or atropine (4×10^{-6} mg/ml) for 3 min before agonist addition. Data were analyzed using GraphPad Prism (version 6) and expressed as mean ± SEM (n = 5), with significance at $P < 0.05$.

Results: The extract produced concentration-dependent uterine contractions comparable to standard agonists at higher concentrations. Atosiban significantly inhibited responses to both oxytocin ($P = 0.011$) and the extract ($P = 0.0001$), indicating oxytocin receptor involvement. Atropine abolished acetylcholine responses but only partially inhibited extract-induced contractions, suggesting partial muscarinic receptor involvement.

Conclusion: The methanol stem extract of TA exerts uterotonic effects via oxytocin receptor activation with additional contribution from muscarinic pathways.

INTRODUCTION

Tacazzea apiculata has been used in the northern Nigeria for induction of labour and the practice has been proven scientifically.[1] The purpose of this study is to establish possible mechanism of action of *Tacazzea apiculata* stem in elucidating uterine contraction.

Induction of uterine smooth muscle contraction involves complex interplay of different signaling mechanisms that include neuronal, endocrine, mechanical, and metabolic processes. The pathways mediated by acetylcholine, oxytocin, histamine, and prostaglandins may be involved, while calcium and other divalent cations and inositol triphosphate play roles as second messengers.[2]

There are mechanisms of action involved in uterine contraction by uterotonic plants.[3] Some of them are connected to the receptors that are present on the uterus such as oxytocin receptor (OTR), prostaglandin F and E receptors (PGF2α and PGE). The cholinergic pathway solely involves muscarinic receptors. Acetylcholine elicits uterine contractile response by acting as an agonist to

muscarinic receptors. Prostaglandin pathways use the synthesis of prostaglandins (the mechanism also used by oxytocin receptors) or stimulation of prostaglandin receptors (PGF2α and PGE), in stimulating uterine contractions. The flow of extracellular calcium through the voltage-gated L- type calcium channels, and intracellular calcium from the sarcoplasmic reticulum, also facilitate myometrial contractions.[4]

Tacazzea apiculata Oliv. family apocyanaceae, commonly known as craw craw in English, Yadiyar kada, yadiyar rafi, yadiya dawa, or simply yadiya in Hausa (Nigeria), Senegal: Badya manta (JB), Basari temba is a woody climber distributed across tropical (Ecuador, Peru) and southern Africa. It thrives in seasonally dry tropical biomes and is recognized in botanical references such as the Kew Plants of the World Online database.[5] The plant is characterized as a liana with opposite glossy leaves, small fleshy flowers, and paired follicles as fruits. Regional floras from southern Africa provide descriptive and photographic documentation for proper identification.[6] Ethnobotanical surveys report widespread use of *Tacazzea apiculata* stem in traditional medicine among Hausa, Fulani, and other ethnic groups in West Africa. Documented uses include treatment of inflammation, hemorrhoids, pain, diabetes, and skin conditions.[7,8]

METHODS

Collection and Identification of Plant Material

Fresh stems of *Tacazzea apiculata* Oliv. (Apocynaceae) were collected from Doka village (GPS coordinates: 10.5875° N, 10.1150° E), Bauchi Local Government, Bauchi state in June, 2021. The stems were dried until a constant weight were attained. The plant was collected by Malam Makama Hamza (a local herbal medicine practioner) and identified and authenticated at the Federal College of Forestry, Jericho, Ibadan, Oyo State by Dr. Samuel A. Odewo, a taxonomist. The specimen sample was kept in the college herbarium and assigned Voucher's number FHI-113439.

Year and Site of Experiment

The experiment was done in the department of Pharmacology and Toxicology, University of Jos, Jos, Nigeria in December, 2022 in the pharmacology laboratory.

Processing of the Plant Material

The stems of *Tacazzea apiculata* Oliv. (Apocynaceae) that has been shade dried to constant weight was triturated with mortar and pestle into powder. 50 g of the powdered *Tacazzea apiculata* stem was subjected to cold methanol maceration extraction by soaking with 500 ml of methanol with intermittent vigorous shaking every 30 minutes for 72 hours to facilitate extraction. The mixture was filtered with white muslin cloth. The filtrate was dried at room temperature until it was fully dried (constant weight). The dried extract was stored in a sample bottle and refrigerated, until it was ready for use.[1]

Drugs and Chemicals

The drugs and chemicals used for the experiment includes Oxytocin (10 iu/ml, Labotocin, Laborate Pharmaceuticals, China), Prostaglandin (5 mg/ml, Lutalyse injection, Zgetis, Zoetis Animal Health), Acetylcholine ($1x10^{-3}$) (Sigma-Aldrich, UK), Estradiol (2 mg/ml Henbel Phango Pharmaceutical co. Ltd) and methanol (Qualilkems Fine Chemicals Pvt Ltd.India),

Experimental Animals

Albino rats (female 180 -200 g) were purchased from the Animal experimental unit of the Department of Pharmacology and Toxicology, University of Jos, Jos, Plateau state, Nigeria. They were housed under standard conditions (23°C±2^{0}C and 12 h light-dark cycle), and allowed free access to water and food. All experiments involving animals were performed according to internationally accepted guide for the care and use of laboratory animals, published by the US National Institutes of Health (NIH Publication No. 85, 23, Revised in 1985).

Ethical Approval

Ethical clearance was obtained from the ethical committee of the Department of Pharmacology and Toxicology, University of Jos. The ethical clearance number was UJ/FPS/F17-0039.

Uterine Tissue Preparation

Healthy female rats were estrogenized by subcutaneous injection of estradiol valerate (0.1 mg/kg) 24 hours prior to the experiment, following the method of Oguntokun et al.[1] Rats were then sacrificed by quick blow on the head, and the uterine horns harvested. The uteri were placed in aerated, warmed De Jalon physiological salt solution containing (g/L): Sodium Chloride (NaCl) 9.0, Glucose 0.5, Sodiumbicarbonate ($NaHCO_3$) 0.5, Magnessium Chloride ($MgCl_2$) 0.006, Potassium Chloride (KCl) 0.42, and Calcium Chloride ($CaCl_2 \cdot 2H_2O$) 0.08. Each uterine horn was mounted in a 25 mL organ bath containing the same solution, maintained at 37°C and aerated with 5% CO_2 in O_2, as described by Bafor et al. (2020).[3] Uterine strips were connected to an isometric force-displacement transducer coupled to PowerLab and LabChart 8 software (AD Instruments, New Zealand) for measurement of

contractions. The transducer was calibrated to correlate force with gauge deflection using a 1 g weight and 1 g load produced a 10 mm deflection on the recording trace (0.1 g/mm). Preparations were equilibrated for 30 minutes prior to administration of extracts or drugs.

Comparison of Responses to the *Tacazzea apiculata* Extract with Uterotonic Agents.

The non-pregnant uterus that has been brought to oestrous by pre-treatment with 0.1 mg/kg estradiol was challenged with other standard drugs like oxytocin, acetylcholine and prostaglandin, after an equilibration period of 30 min, normal myometrial contractions were recorded at baseline. Uterine contractile responses were elicited by adding oxytocin (2×10^{-3}- 3.2×10^{-2}) mg/ml, acetylcholine (1.6×10^{-8} – 2.56×10^{-7}) mg/ml, prostaglandin (3.2×10^{-10} -5.12×10^{-9}) mg/ml and methanol extract of *Tacazzea apiculata* (4×10^{-3} – 1.28×10^{-1}) mg/ml to the De Jalon's solution.[1] Each dose of the drug and extract was allowed to act for 1 min and the amplitude of the contraction recorded by means of a force transducer and normal uterine smooth muscle contractions were recorded using an 8-channel recorder (Power Lab, model 8/30, AD Instruments, Australia). The amplitude of the crude extract and the standard drugs were compared by comparing their means using one –way ANOVA using SPSS version 26. All curve fitting and comparisons were performed using GraphPad Prism (version 6). Statistical significance was accepted at $P < 0.05$. Results are presented as mean ± SEM of n = 5 independent experiments.

Determination of the Mechanism of Action of *Tacazzea apiculata* Extract in Elucidating Uterine Contraction

Each preparation was subjected to a resting tension of 1.0 g and allowed to equilibrate for 30 min before it was challenged with the extract of *Tacazzea apiculata*. After an equilibration period of 30 min, normal myometrial contractions were recorded at baseline. Uterine contractile responses were elicited by adding oxytocin (6.64×10^{-6} - 53 $\times 10^{-5}$) mg/ml, acetylcholine (4×10^{-7}- 16×10^{-7}) mg/ml, prostaglandin (2×10^{-6} - 16×10^{-6}) mg/ml and methanol extract of *Tacazzea apiculata* (0.08 – 0.64) mg/ml to the De Jalon's solution. Each dose of the drug and extract was allowed to act for 3 min and the amplitude of the contraction recorded by means of a pressure transducer and normal uterine contractions were recorded using an 8-channel recorder (Power Lab, model 8/30, AD Instruments, Australia). Atosiban (4×10^{-5} mg/ml) was used to antagonise the responses of the isolated uterus to oxytocin, prostaglandin and the crude extract ,[9] Atropine (4×10^{-6} mg/ml) was used to antagonize the responses of the isolated uterus to acetylcholine and the crude extract. The method of Ngadjul was adopted.[10]

Statistical Analysis

Data were analyzed using GraphPad Prism 6 (Version 6.01, GraphPad Software Inc., CA, USA). Results are presented as mean ± standard error of the mean (SEM) from five replicates (one strip from one animal). Comparisons were performed using Student's t-test or one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. Differences were considered statistically significant at $P < 0.05$.

RESULT

Comparison of agonists revealed that acetylcholine and prostaglandin produced comparable maximal uterine contractile responses, with no marked difference in efficacy. Prostaglandin demonstrated the highest potency, followed by acetylcholine. Although the plant extract exhibited lower potency, it produced a greater maximal response than oxytocin, indicating high efficacy. These findings suggest that the extract acts as a strong uterotonic agent, possibly via multiple receptor-mediated pathways.

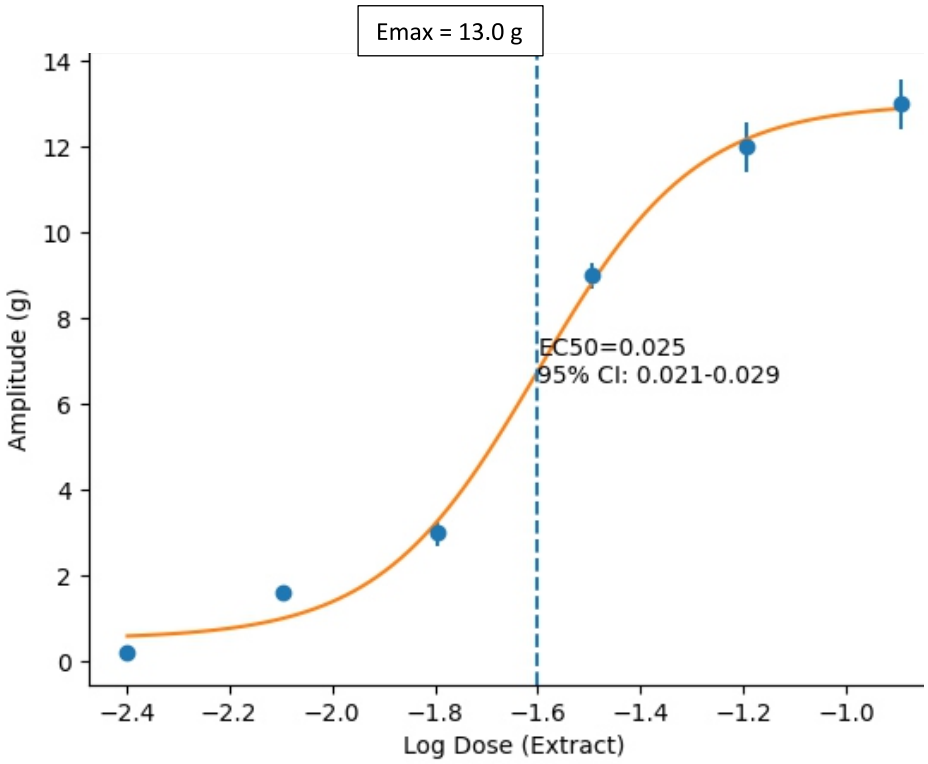

Figure 1 Log dose–response curve of methanol extract of *Tacazzea apiculata* on isolated uterine strips of albino rats. Data were fitted using a four-parameter logistic model. The extract produced a concentration-dependent increase in amplitude with an Emax of approximately 13 g and an EC_{50} (half maximal effective concentration) of 0.025 mg/mL (95% CI: 0.021–0.029 mg/mL).

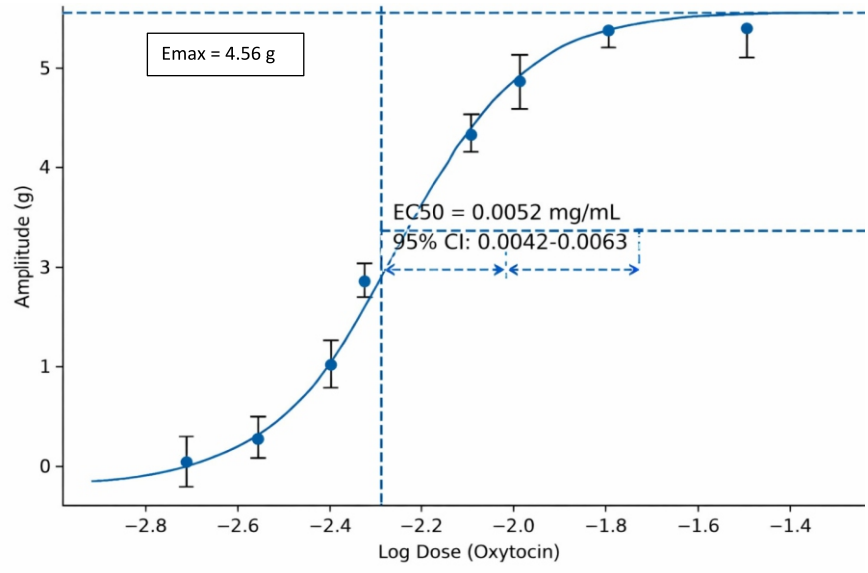

Figure 2 Log dose–response curve of oxytocin on isolated uterine strips of albino rats. Data were fitted using a four-parameter logistic model. Oxytocin produced a concentration-dependent increase in contractile amplitude with an Emax of approximately 4.56 g and an EC_{50} of 0.0052 mg/mL (95% CI: 0.0042–0.0063 mg/mL).

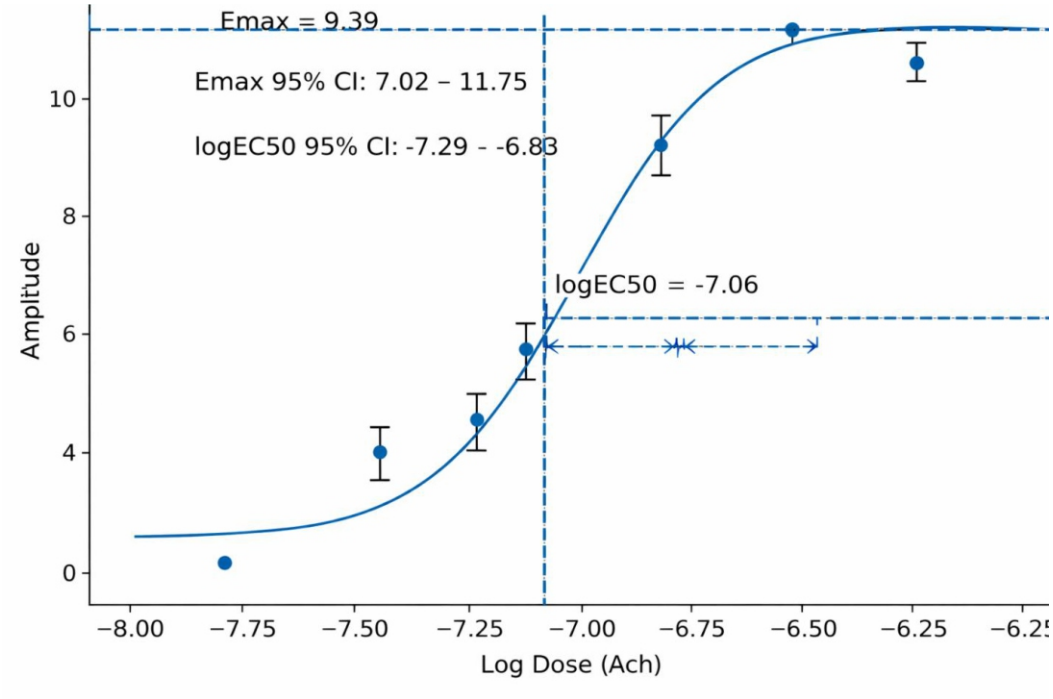

Figure 3 Acetylcholine produced a concentration dependent increase in uterine contractility with a maximal effect (Emax) of approximately 9.5 units and a half-maximal effective concentration ($logEC_{50}$) of about −7.06.

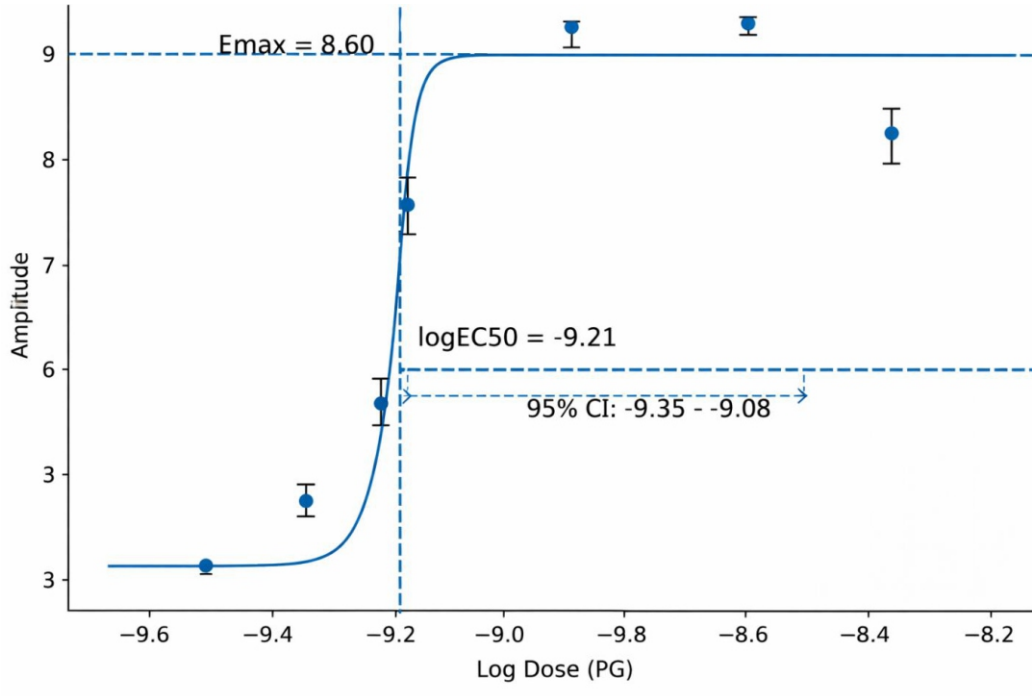

Figure 4 Prostaglandin produced a concentration-dependent increase in uterine contractile response with a maximal effect (Emax) of 8.6. The $logEC_{50}$ was –9.21, indicating high potency. 95% CI: 6.89 – 10.31 and $EC_{50} \approx 6.16 \times 10^{-10}$

Comparision of EC50 and Emax of the Extract with the Standard Dugs

The prostaglandin was the most potent while the extract was the least potent as detailed in Table 1 below.

Table 1: Comparision of EC_{50} and Emax of standard Dugs with the Extract's EC_{50} and Emax.

Agonist	Emax (g)	Log EC_{50}	Extract Vs SD P - Values	Potency (EC_{50}) values
Prostaglandin	8.60 ± 0.00*	-9.21 Ω	0.022	Most potent
Acetylcholine	9.39 ± 0.58*	-7.06 Ω	0.013	Moderately
Oxytocin	4.46 ± 0.06 *	-2.28 Ω	0.004	Less potent
Extract	13.00 ± 0.58	-1.60	> 0.05	Least potent

Keys: SD – Standard drugs,* $P < 0.05$ extract Emax versus standard drugs Emax; Ω $P < 0.05$ EC_{50} standard drugs versus extract. Values represent mean ± SEM of maximal contractile responses (Emax) obtained from isolated uterine strips (n = 5 preparations per group). Statistical comparisons were made using unpaired Student's t-test with Welch's correction. $P < 0.05$ was considered statistically significant.

The Inhibitory Effects of Atosiban on Oxytocin and *Tacazzea apiculata* extract

Uterine smooth muscle contractions stimulated by oxytocin (6.64×10^{-6} - 53×10^{-6}) mg/ml and *Tacazzea apiculata* (0.04 – 1.28) mg/ml were inhibited (*P*- values; 0.011 and 0.0001) respectively by atosiban (4×10^{-5}) as depicted in Figures 5-8 below.

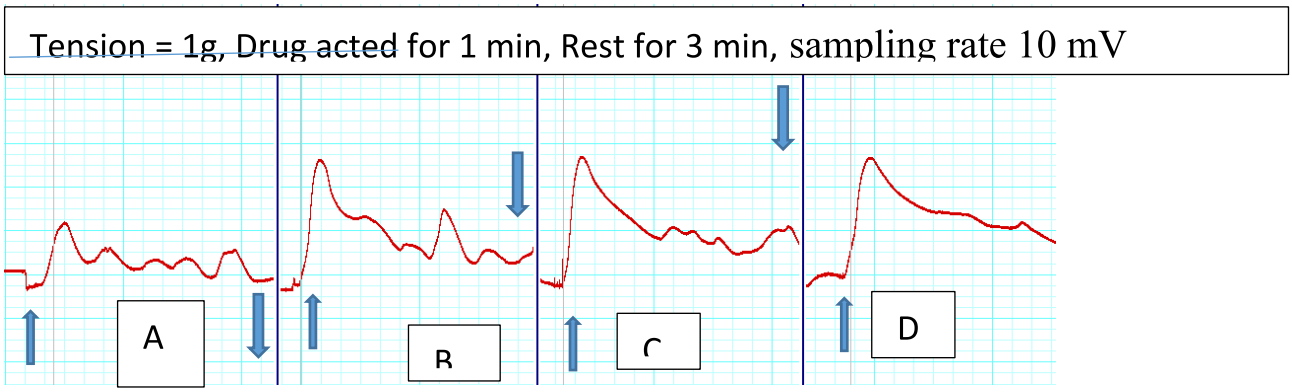

Figure 5: Representative uterine contraction traces showing the effect of oxytocin on isolated rat uterine strips. Oxytocin (6.64×10^{-6}–5.3×10^{-4}) mg/ml was added at the time points indicated by faint vertical lines, producing concentration-dependent increases in contractile force. Thick vertical lines indicate washout periods. Each trace is representative of responses obtained from uterine strips from five animals, and data are expressed as mean ± SEM. Keys ⬇ – Washing; ⬆ Addition of Drug A: OT 6.64×10^{-6} mg/ml B: OT 1.33×10^{-5} mg/ml C: OT 2.65×10^{-5} mg/ml D: OT 5.3×10^{-5} mg/ml

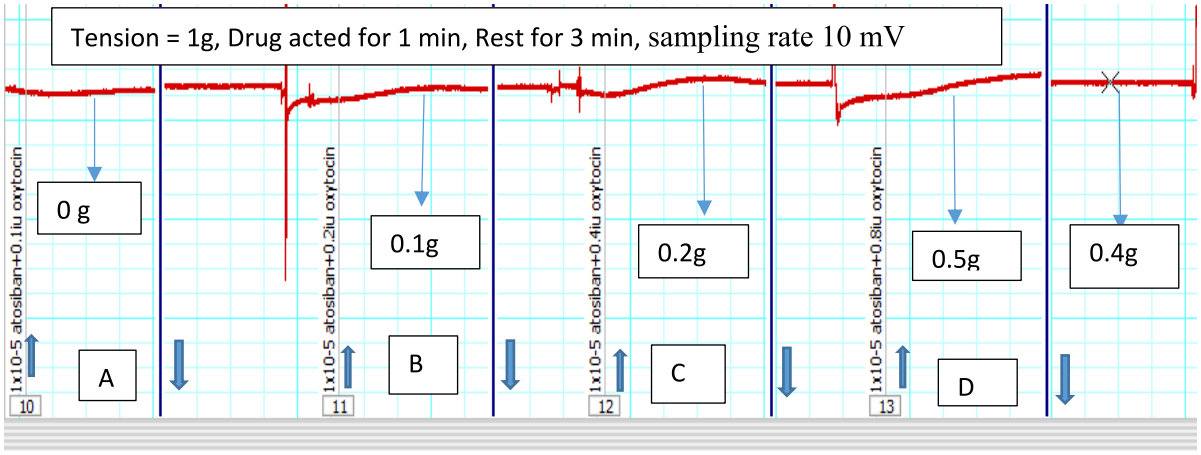

Figure 6 Inhibitory Effect of Atosiban (4 x 10^{-5}) mg/ml on Oxytocin (OT) (6.64 x 10^{-6} - 5.3 x 10^{-5}) mg/ml Induced Uterine Smooth Muscle Contraction

Keys: ⇓-Washing; ⇑ – Addition of Drug
A: (Atosiban 4 x 10^{-5} + OT 6.64 x 10^{-6}) mg/ml
B: (Atosiban 4 x 10^{-5} + OT 1.33 x 10^{-5}) mg/ml
C: (Atosiban 4 x 10^{-5} + OT 2.65 x 10^{-5}) mg/ml
D: (Atosiban 4 x 10^{-5} + OT 5.3 x 10^{-5}) mg/ml

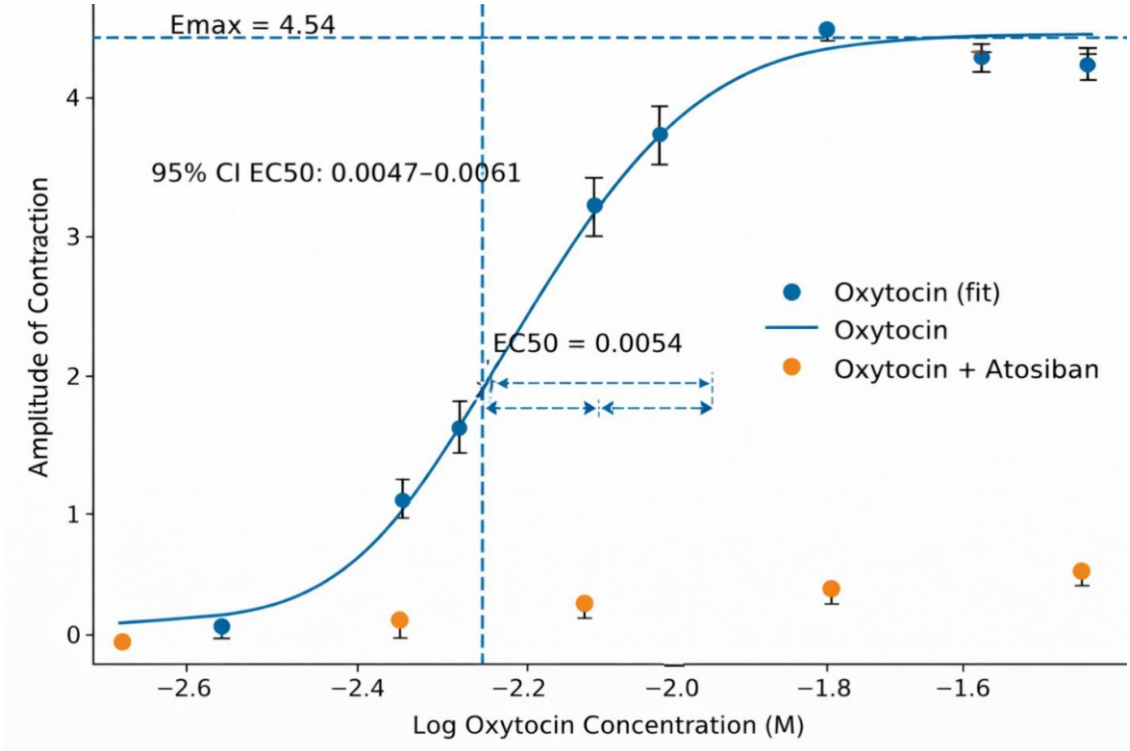

Figure 7 Atosiban almost completely abolished oxytocin-induced uterine contractions. This represents functional antagonism with complete suppression of Emax, rather than a curve shift.

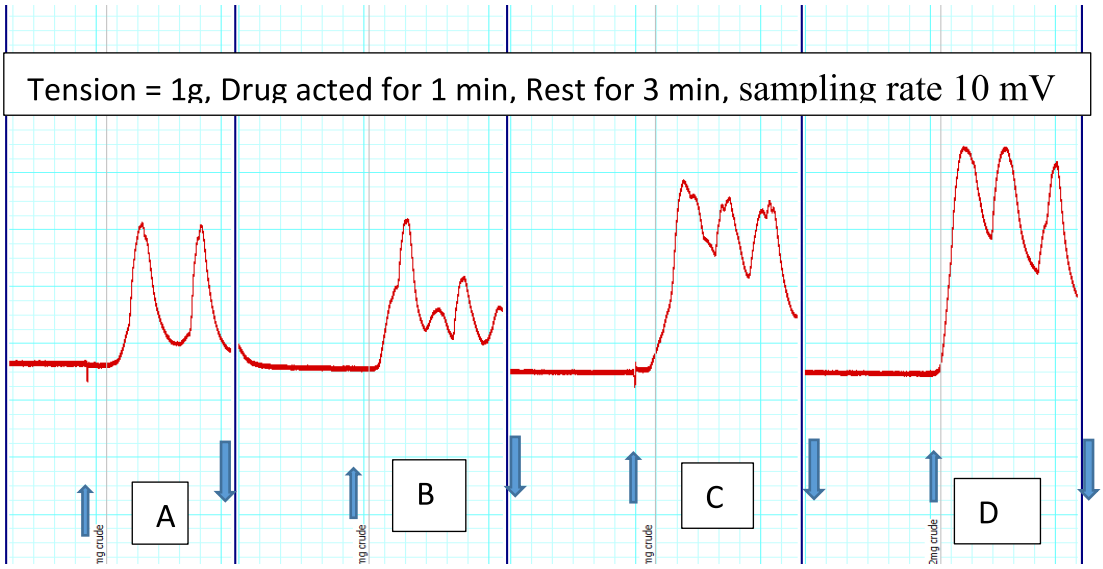

Figure 8 Tacazzea *apiculata* (TA) Extract (0.08 – 0.64) mg/ml Induced Uterine Smooth Muscle Contractions

Keys: Thick line – Washing; Thin line – Addition of Drug
A: TA 0.08 mg/ml B: TA 0.16mg/ml C: TA 0.32 mg/ml
D: TA 0.64 mg/ml

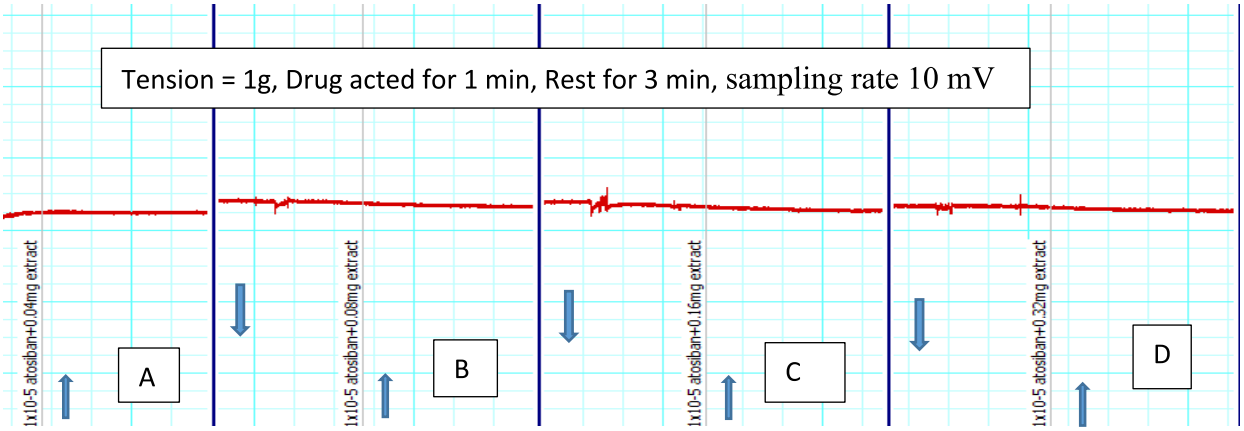

Figure 9 Inhibitory Effect of Atosiban (4 x 10^{-5}) mg/ml on *Tacazzea apiculata* Extract (0.04 – 1.28) mg/ml Induced Uterine Smooth Muscle Contractions

Keys: Thick line – Washing; – Addition of Drug
A: (Atosiban 4 x 10^{-5} + TA 0.04) mg/ml
B: (Atosiban 4 x 10^{-5} + TA 0.08) mg/ml
C: (Atosiban 4 x 10^{-5} +TA 0.16) mg/ml

D: (Atosiban 4 x 10^{-5} + TA 0.32) mg/ml

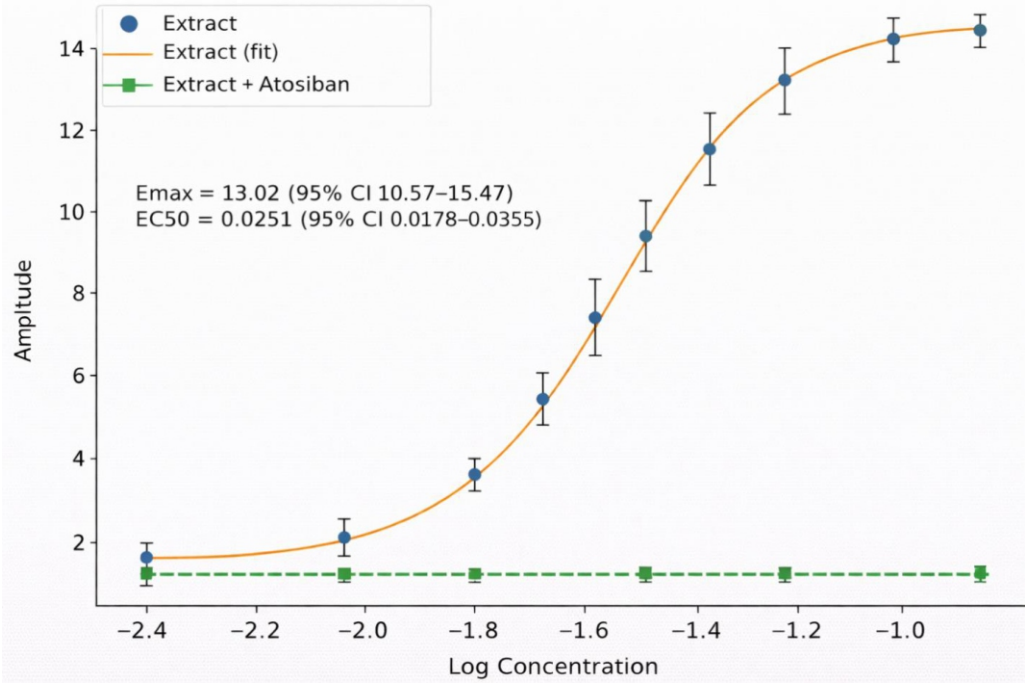

Figure 10 Inhibitory effect of Atosiban on Extract induced Uterine contractionAtosiban completely abolished extract-induced uterine contractions. This represents functional antagonism with complete suppression of Emax, rather than a curve shift.

Effect of Atosiban on Prostaglandin Induced Uterine Smooth Muscle Contraction

Also, the contractile effect of the prostaglandin (2 x 10^{-6} – 16 x 10^{-6}) mg/ml on the uterus was inhibited by atosiban as shown in Figures 10-11.

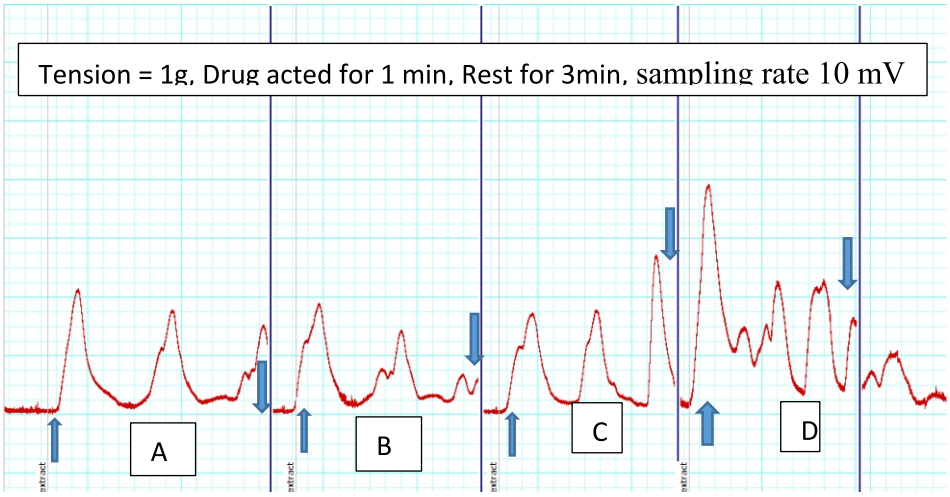

Figure 11 Prostaglandin (PG) (2 x 10^{-6} - 16 x 10^{-6}) mg/ml Induced Uterine Smooth Muscle Contraction

Keys: Thick line – Washing; Thin line – Addition of Drug
A: PG 2 x 10^{-6} mg/ml B: PG 4 x 10^{-6} mg/ml
C: PG 8 x 10^{-6} mg/ml D: PG 16 x 10^{-6} mg/ml

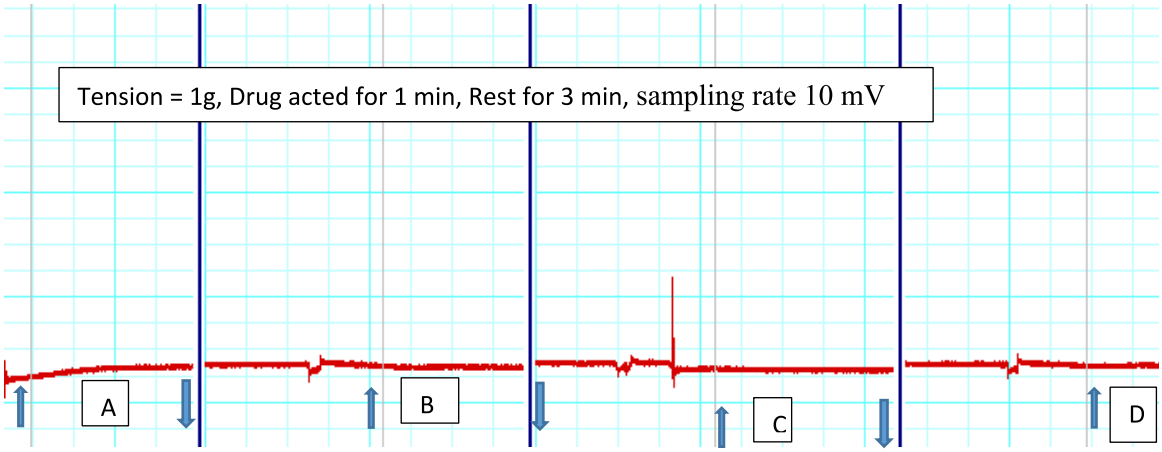

Figure 12 Inhibitory Effect of Atosiban (4 x 10^{-5}) mg/ml on Prostaglandin (PG) (2 x 10^{-6} - 16 x 10^{-6}) mg/ml Induced Uterine Smooth Muscle Contraction

Key: Thick line – Washing; Thin line – Addition of Drug

A: (Atosiban 4 x 10^{-5} + PG 2 x 10^{-6}) mg/ml

B: (Atosiban 4 x 10^{-5} + PG 4 x 10^{-6}) mg/ml

C: (Atosiban 4 x 10^{-5} + PG 8 x 10^{-6}) mg/ml

D: (Atosiban 4 x 10^{-5} + PG 16 x 10^{-6}) mg/ml

Effect of Atropine on Acetylcholine and *Tacazzea apiculata* Induced Uterine Smooth Muscle Contraction

The contractile effect of acetylcholine (4 x 10^{-7}- 16 x 10^{-7}) mg/ml on the uterus was inhibited (p –values = 0.014) by atropine (4x10^{-6} mg/ml), a muscarinic receptor antagonist which also insignificantly inhibit the contractile effect of *Tacazzea apiculata* (0.04 – 0.08) mg/ml on the uterus (Figure 11).

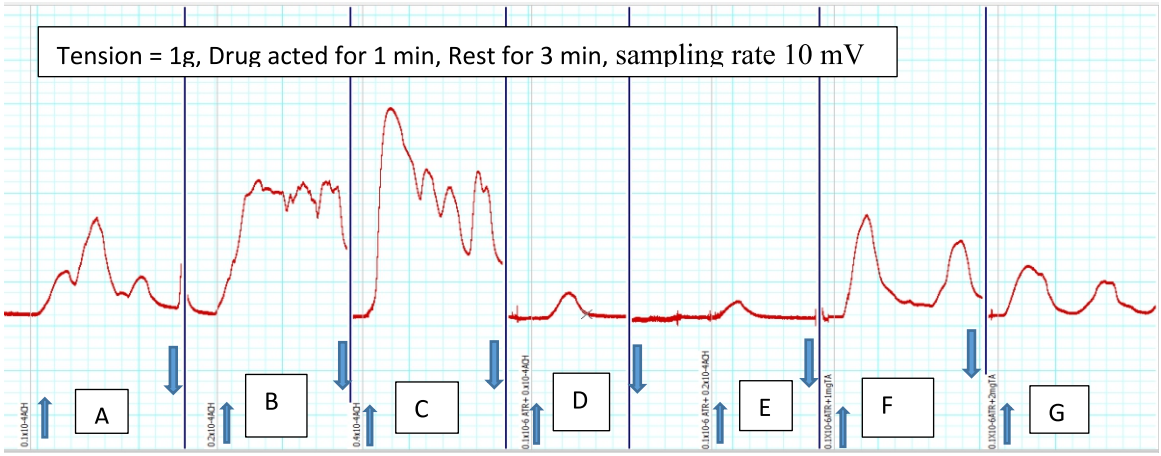

Figure 13 The Inhibitory Effect of Atropine (Atr) (4 x 10^{-6}) mg/ml on Acetylcholine (Ach) (4 x 10^{-7}- 16 x 10^{-7}) mg/ml and *Tacazzea apiculata* (0.04 – 0.08) mg/ml induced Uterine Smooth Muscle Contractions

Keys: Thick line – Washing; Thin line – Addition of Drug

A: Ach 4 x 10^{-7} mg/ml B: Ach 8 x 10^{-7} mg/ml C: Ach 16 x 10^{-7} mg/ml

D: (Atr 4 x 10^{-6} + Ach 4 x 10^{-7}) mg/ml E: (Atr 4 x 10^{-6} + Ach 8 x 10^{-7}) mg/ml

F: (Atr 4 x 10^{-6} + TA 0.04) mg/ml G: (Atr 4 x 10^{-6} + TA 0.08) mg/ml

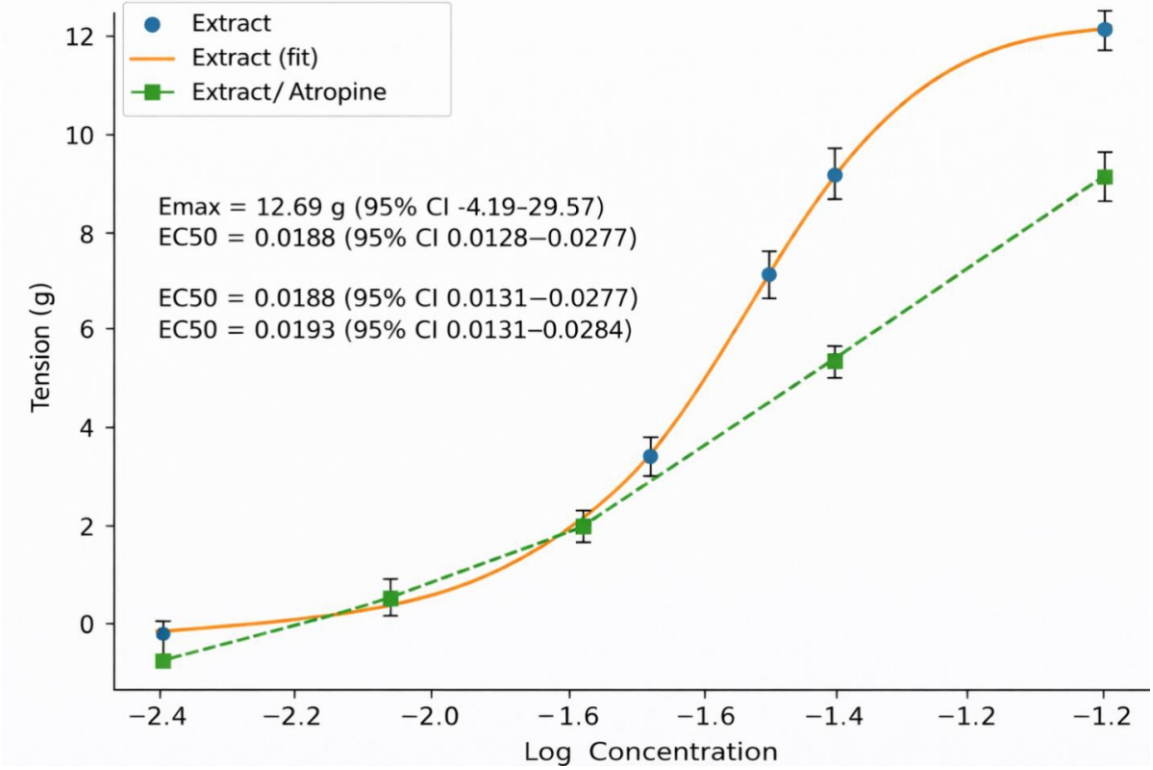

Figure 14 Inhibitory effect of atropine on uterine contractility of the Extract

There is no statistically significant difference between the extract concentration response curve in the absence and presence of atropine (P = 0.144). Atropine produced a partial reduction in maximal response without a statistically significant shift of the overall curve. The Emax and EC_{50} is for the extract in the absence of atropine

Discussion

The qualitative phytochemical analysis of the methanol extract of TA revealed the presence of the following phytochemical constituents: Flavonoids, alkaloids, tannins, saponins, cardiac glycosides, steroids, quinones and terpenoids. Components of TA phytochemicals have been shown to possess uterine stimulating effect.[1] The present study demonstrates differential potency and efficacy among acetylcholine, prostaglandin, oxytocin, and the methanol extract of *Tacazzea apiculata* on isolated uterine strips. Prostaglandin exhibited the highest potency, consistent with activation of prostaglandin F receptor (FP) and prostaglandin E receptor (EP) receptors, which are known to directly increase intracellular Ca^{2+} levels and enhance myometrial sensitivity to calcium, resulting in powerful uterine contractions. Acetylcholine also showed high potency and efficacy, likely mediated through muscarinic M_3 receptors coupled to phospholipase C activation and inositol trisphosphate–dependent Ca^{2+} release.[2,11]

Oxytocin produced a comparatively lower maximal response in this experimental preparation despite its established clinical potency. This finding may be attributed to receptor desensitization, tissue variability, or dependence on prostaglandin synthesis for full uterotonic expression. Oxytocin receptor activation is known to stimulate both direct Ca^{2+} influx and secondary prostaglandin release, suggesting functional interaction between oxytocin and prostaglandin pathways.[11] Interestingly, the plant extract displayed lower potency but greater maximal efficacy than oxytocin, indicating that once an effective concentration is achieved, it produces strong uterine contraction. This pharmacological profile is characteristic of crude plant extracts and suggests the presence of multiple bioactive constituents acting synergistically. The extract may exert its uterotonic effect through simultaneous modulation of oxytocin receptors, prostaglandin synthesis pathways, and cholinergic mechanisms, thereby amplifying uterine contractility. Overall, these findings support the ethnomedicinal use of *Tacazzea apiculata* as a uterotonic agent and provide mechanistic evidence that its activity may involve oxytocin, muscarinic and prostaglandin dependent signaling pathways. Previous studies have shown many plants possess uterotonic activity similar to the plant under study eliciting uterine activity at higher concentrations

compared with standard drugs. Such plants include *Euphorbia heterophylla* leaves (Ewe ọlọmọ),[12] *Spondias mombin* (Iyeye, Uchịrị, Tsadar masar) [13], *Azanza garckeana* (African chewing gum tree, Goron tula) [14], *Launaea taraxacifolia* (Yanrin, African lettuce, Ugu oyibo) [15], *Uvariodendron kirkii* (Not well documented in Nigeria) [16], *Steganotaenia Araliacea* (Carrot tree) [17], *Sida corybomsa* (Wireweed, Ìsẹ̀pẹ̀) [18], *Phytolacca dodecandra* (African soapberry) [19], *and Monechema ciliatum* [20].

In the current study, **atosiban,** a selective **oxytocin receptor antagonist**, was employed to assess the mechanism of uterine stimulation induced by **oxytocin, prostaglandin, and methanol extract of *Tacazzea apiculata* (TA)** in an **estrogen-primed uterus.** The pre-treatment with oestradiol ensured upregulation of oxytocin receptors on uterine smooth muscle, thus optimizing the uterus for contractile responses.[11] Atosiban is a non-peptide oxytocin receptor antagonist that competitively inhibits the binding of oxytocin to its receptors on the myometrial surface. It also has an antagonistic effect on vasopressin V1a receptors, which are structurally similar to oxytocin receptors. Clinically, atosiban is used as a **tocolytic agent** to delay preterm labor by inhibiting uterine contractions[21]. As expected, the administration of atosiban **significantly inhibited the contractile response induced by exogenous oxytocin** in the estrogenized uterus. This result confirms that the uterine contractions induced by oxytocin are mediated specifically through **oxytocin receptors,** and that atosiban effectively blocks this pathway, validating its role as a standard inhibitory control in uterotonic studies [22]. Interestingly, atosiban also **attenuated the contractile responses induced by prostaglandin F2α**. This may be due to **cross-talk between oxytocin and prostaglandin signaling pathways,** as oxytocin has been shown to stimulate prostaglandin synthesis in the uterus. Additionally, oxytocin and prostaglandins can converge on **common intracellular signaling cascades,** particularly those involving phospholipase C, inositol triphosphate (IP3), and calcium release [11].

In contrast, co-administration of atosiban (4×10^{-5} mg/ml) completely abolished the contractile responses to the extract across all tested concentrations, as evidenced by the flat concentration–response profile with near-zero amplitude. The absence of any upward trend or residual contractile activity strongly suggests that the uterotonic effect of the extract is critically dependent on oxytocin receptor activation. This finding implies that constituents of the extract either directly stimulate oxytocin receptors or enhance downstream oxytocin receptor signaling pathways. The profound inhibitory effect of atosiban is particularly noteworthy because it suggests a dominant oxytocinergic mechanism rather than partial involvement. In many plant-derived uterotonics, antagonist exposure often produces a rightward shift or partial reduction in Emax; however, the near-complete suppression observed here indicates that oxytocin receptor signaling is likely the primary pathway mediating the extract's effect. This interpretation is consistent with the established role of oxytocin receptors in uterine contraction via phospholipase C activation, inositol trisphosphate generation, and intracellular calcium mobilization [2].

Furthermore, the clear separation between the extract control curve and the extract + atosiban curve supports statistical differentiation of the responses. Formal curve comparison using the extra sum-of-squares F-test confirmed a significant difference between the two conditions, strengthening the mechanistic conclusion that oxytocin receptor blockade eliminates extract-induced uterine contraction. From a pharmacological and ethno pharmacological perspective, these results provide strong experimental support for the traditional use of TA in reproductive health. However, the potent oxytocin-like activity observed also raises important safety considerations, as excessive uterine stimulation may pose risks if used indiscriminately during pregnancy. This underscores the need for further studies to isolate and characterize the active constituents, determine receptor selectivity, and evaluate dose-dependent safety margins.

Notably, phytochemicals like **saponins, steroids, and flavonoids** found in the extract are known to influence uterine activity via **hormonal or receptor-mediated pathways,** including oxytocin modulation. [1,23,24] The ability of atosiban to inhibit contractions induced not only by oxytocin but also by prostaglandin and TA extract indicates a **shared or overlapping pathway of action,** likely involving **oxytocin receptor activation and calcium-dependent signaling**. This suggests that the **uterotonic effect of** TA is at least **partly receptor-dependent**, and further mechanistic studies are warranted to identify the specific phyto-constituents responsible. This was in conformity with the inhibitory effect of atosiban on uterine contractile activity of *Lannea acidia* suggesting mediation of its uterine contraction via the oxytocin receptor just like the plant under study.[10]

Previous studies have shown the presence of cholinergic receptor mainly M3 muscarinic type on uterus smooth muscle and that stimulation of this receptor by agonist such as acetylcholine (Ach) enhances uterine contraction.[11] Also, the effect of the plant on muscarinic receptors was evaluated. Uterus was pretreated with atropine a non-specific muscarinic receptor (M_3) antagonist known for

smooth muscle relaxation to inhibit the contractile effects of both Ach and TA The contractile effect of Ach was significantly inhibited while that of the TA was insignificantly inhibited by atropine. In the presence of atropine (muscarinic receptor antagonist), the curve showed a marked reduction in maximal response and a rightward shift, indicating inhibition of the extract-induced contractions. A reduction in Emax suggests a non-competitive or mixed antagonistic effect, while a parallel rightward shift without loss of Emax would indicate competitive antagonism [25]. These observations imply that the uterotonic activity of *Tacazza apiculata* is mediated, at least in part, through oxytocin and/or muscarinic receptor pathways.

CONCLUSION: Methanol extract of *Taccazea. apiculata* stem exerts uterotonic activity through oxytocin receptor interaction, prostaglandin pathway and partially dependent on muscarinic receptor pathways. These findings validate its traditional use in labour induction and provide a pharmacological basis for further bioactive compound isolation.

ACKNOWLEDGEMENTS

I am grateful to Professor Olayinka Ogunleye, Professor Oladipupo Ogunleye, for the financial support. I am grateful to Mr Holleng Madaki, Mr Bulus Diyen and all the staff of department of Pharmacology laboratory for their technical support. My appreciation goes to Mr Wazo Lukas and Mr Zema Danladi for taking care of the experimental animals and making them available.

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