In-Vitro effect of Ficus deltoidea on the contraction of isolated rat’s uteri is mediated via multiple receptors binding and is dependent on extracellular calcium

Naguib Salleh* and Vivi Noryati Ahmad

Abstract

**Background:** Ficus deltoidea, is a perennial herb that is used to assist labor, firm the uterus post-delivery and to prevent postpartum bleeding. In view of its claimed uterotonic action, the mechanisms underlying plant’s effect on uterine contraction were investigated.

**Methods:** Adult female SD rats were injected with 2 mg/kg 17β-oestradiol (E2) to synchronize their oestrous cycle. A day after injection, uteri were removed for in-vitro contraction studies. The dose dependent effect of Ficus deltoidea aqueous extract (FDA) on the tension produced by the isolated rat’s uteri was determined. The effects of atropine (2×10^-8 M), atosiban (0.5 IU), THG113.31 (10 μM), oxodipine (0.25 mM), EDTA (1 mM), 2-amino-ethoxy-diphenylborate (2-APB) (40 mM) and thapsigargin (1 mM) on the maximum force of contraction (Emax) achieved following 2 mg/ml FDA administration were also investigated.

**Results:** FDA induced in-vitro contraction of the isolated rat’s uteri in a dose-dependent manner. Administration of atropine, atosiban and THG113.31 reduced the Emax with atosiban having the greatest effect. The Emax was also reduced following oxodipine and EDTA administration. There was no significant change observed following 2-APB administration. Thapsigargin, however, augmented Emax.

**Conclusions:** FDA-induced contraction of the isolated rat’s uteri is mediated via multiple uterotonin receptors (muscarinic, oxytocin and prostaglandin F2α) and was dependent on the extracellular Ca^{2+}. Contraction, however, was not dependent on the Ca^{2+} release from the internal stores. This in-vitro study provides the first scientific evidence on the claimed effect of Ficus Deltoidea on uterine contraction.

**Keywords:** Ficus deltoidea, Uterotonin receptors, Extracellular Ca^{2+}

Background

Uterotonic plants, are plants that stimulate uterine contraction and have been used since the ancient times to assist labor, remove the retained placenta, treat post partum bleeding and as an abortifacient [1]. Despite their use, scientific evidence to substantiate their beneficial effects are still being explored. Several plant extracts have been reported to induce uterine contraction which include the leaves extract of P. nigrescens, C. bondoc and A. africanus [2-4], roots extract of C. papaya [5,6] and L. pumila [7] and several other extracts from various plant species [8,9].

One of the plants that is popularly used among the Southeast Asian women to induce uterine contraction is Ficus deltoidea, which belongs to the family Moraceae [10]. Ficus deltoidea has been claimed to possess uterotropic properties that can assist labor as well as can promote involution of the uterus, cervix and vagina during the postpartum period. In addition, it has also been used to treat abnormalities in the menstrual cycle and for birth spacing purposes. Ficus deltoidea is a small perennial herb which rarely exceeds 2 meters in height and is domestically cultivated. It is known by various names such as Mas
Cotek in Malaysia, Tabat Barito in Indonesia, Agoluran in The Philippines and Kangkalibang in Africa [11]. Different sub-species can be identified based on the leaf shape; with the female plants possessing larger and more round leaves, whereas the males are smaller with long and round leaves [12]. All parts of this plant are medicinally useful. The leaves (when boiled), stems, roots and fruits are traditionally used to treat arthritis, boost the immune system and increase the sexual desire [13]. Additionally, the leaves are also claimed to be a powerful fat burner, help to decrease plasma cholesterol level and are experimentally proven to lower the blood glucose level [14]. Recently, the fruit extract of Ficus deltoidea was found to possess antidiabetic and antioxidant properties [15].

The notion that Ficus deltoidea affects uterine contraction was based on several previous studies involving other Ficus species which also indicate their effect on the uterine contractility. Most of these studies were conducted in-vitro using isolated uteri from rodents. Bafor et al. [16] conducted an in-vitro study using isolated strips of mouse uteri to investigate the effect of the active constituent of Ficus exasperata leaf extract on uterine contraction. They have found that metabolites generated from this extract possess both tocolytic and uterotonic activities. Earlier, in-vitro contraction studies using isolated rat’s uteri revealed both stimulatory [17] and inhibitory [18] effects of the unpurified extract of Ficus exasperata. Further to this, Watcho et al., [1] demonstrated that fruit extract of Ficus asperifolia stimulates in-vitro contraction of the uteri isolated from oestrogenized rats. Another Ficus species, Ficus capensis was shown to inhibit in-vitro contraction also in the isolated rat’s uteri [19]. In view of the fact that Ficus species was found to affect uterine contractility, we hypothesized that Ficus deltoidea, which is also from the Moraceae family, may affect uterine contraction as traditionally claimed. Therefore, using similar experimental model [1,17,18,20], we investigated Ficus Deltoidea effect on uterine contraction.

Methods
Preparation of F. Deltoidea Aqueous extract (FDA)
Leaves of F deltoidea from female sub-species used in this study were supplied by Delto Medicama Plantation, Kuala Selangor, Malaysia. The plant sample was deposited at the Herbarium in Rimba Ilmu, University of Malaya, Kuala Lumpur for authentication and identification purposes with Herbarium number: KLU 46469. The leaves were air-dried, cut into small pieces and grounded into powder form. Each of the pulverized parts were weighed (100 grams) and boiled twice in 1 litre distilled water for 4 hours. The aqueous extract was then concentrated by heating at 60°C and was later subjected to freeze-drying (yield 7.36% and 11.61% w/w, dry weight basis for leaf) and was stored in a container until further use. Stock solution was obtained by dissolving small aliquots of this extract in water.

Uterine tissue preparation and In-Vitro contraction study
Adult female Wistar Kyoto (WKY) rats weighing 250 grams were purchased from the Animal House, Faculty of Medicine, University of Malaya, Kuala Lumpur. The rats were housed in a controlled environment with temperature kept at 25°C, relative humidity between 30–70%, 12 hours light–dark cycle and had free access to rodent food pellet and tap water ad libitum. Cleanliness of the housing environment was maintained daily. Shredded recycled paper was used as bedding. Each group consists of six rats (n = 6). All experimental procedures were approved by the University of Malaya Medical Center Animal Ethics Committee (Ethics Reference No: FIS/ 01/12/2008/ NS (R)).

Intact, non-ovariectomised female WKY rats were treated with high dose of E2 at 2 mg/kg/day to synchronize their oestrous cycle [17]. A day after injection, the rats were humanely sacrificed and the uteri were immediately removed and placed into a physiological solution. The tissue was then placed vertically in an organ bath containing solution with the following electrolytes composition: NaCl (155 mM), KCl (4.5 mM), MgCl2 (1.0 mM), CaCl2 (2.0 mM) and D-glucose (10 mM) while the pH was maintained at 7.40 with NaOH. The temperature of the organ bath was maintained at 37°C. 95% O2 and 5% CO2 was continuously delivered into the bathing solution. Each uterine strip was placed under optimum resting force of 1 g and was allowed to equilibrate for 30 minutes prior to drug administration. During this period, the strips were washed with 10 ml fresh physiological solution every 15 minutes according to the method by Oropeza et al., [21]. Each experiment was repeated six times using new uterine strips from different rats (n = 6). Contractile forces were recorded isometrically by a force transducer which was connected to a bridge amplifier and to the PowerLab data acquisition system (ADI Instrument, Australia).

FDA was added in a dose-dependent manner (0.125–4.0 mg/ml) and the dose-response effect was then recorded. Preliminary investigation revealed that 1 × 10^{-2} M Ach (Sigma-Aldrich), 7 I.U. oxytocin (Sigma-Aldrich) and 5 μg/ml PGF2α (Sigma-Aldrich) produced maximum force of contraction (Emax), which values differ between the respective agonists. Meanwhile, 2 mg/ml FDA also resulted in maximum contraction (Emax), however with a lower Emax than other tested agonists. Atropine (Sigma-Aldrich) (2 × 10^{-8} M), a muscarinic receptor antagonist; atosiban (Fluka Co) (0.5 IU), an oxytocin receptor antagonist, THG113.31 (Theratechnologies) (10 μg/ml), a PGF2α receptor antagonist, oxodipine (Sigma-Aldrich) (0.25 μM), an L-type Ca^{2+}-channel blocker, 2-APB (Sigma
Aldrich) (40 μM), an IP₃ receptor (IP₃R) blocker, thapsigargin (Sigma Aldrich) (1 μM), a sarcoplasmic reticulum Ca²⁺-ATPase (SERCA) inhibitor and EDTA (Sigma Aldrich) (1 mM), a Ca²⁺ chelator were administered to investigate the mechanism underlying FDA effect on uterine contraction. In order to observe the effect of these inhibitors, 2 mg/ml FDA was initially added into the bathing solution and once contraction was stable at Emax, these inhibitors were either individually or simultaneously added and their effects on the Emax were then recorded.

**Statistical analysis**
Results were expressed as mean ± SEM. Data was analyzed using Student’s t-test. p < 0.05 was considered to be statistically significant.

**Results**

**Dose-dependent effect of FDA on uterine contraction**
In Figure 1, the force of contraction increases with increasing doses of FDA. In the control group, the force recorded was 0.5 ± 0.05 g tension, which was the baseline contraction in oestrogenized rats’ uteri. At 0.25 mg/ml, the force generated was 2.4 times greater than the control. Meanwhile, the forces increase by 3.0, 4.1 and 4.9 times following administration of 0.5, 1 and 2 mg/ml FDA respectively with 2 mg/ml FDA produced the maximum tension (Emax).

**Effect of atropine, THG113.31 and atosiban on the Emax induced by 2 mg/ml FDA**
In Figure 2, administration of muscarinic receptor antagonist, atropine, into the bathing solution containing isolated uterine tissue pre-exposed to 2 mg/ml FDA resulted in the Emax to decrease by 1.19 times. Meanwhile, administration of THG113.31, a non-competitive inhibitor for PGF2α receptor, as well as atosiban, an oxytocin receptor blocker resulted in the Emax to also decrease by 1.32 and 1.60 times respectively. Simultaneous administration of atropine, atosiban and THG113.31 resulted in 4.45 times decrease in Emax as compared to 2 mg/ml FDA administration alone.

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**Figure 1 The effect of FDA on uterine contraction.** (a) Tracing of isometric uterine contraction following administration of various doses of FDA and (b) mean tension generated from six isolated uterine horns obtained from different oestrogenized rats, which were exposed to various doses of FDA at concentrations ranging between 0.125 to 4 mg/ml. There was a dose-dependent increase in the tension with increasing doses of FDA. The tension recorded following administration of 2 mg/ml FDA was 4.9 times higher than the control. n = 6 (* p < 0.05 as compared to control).
Relative potency of FDA as uterotonin

In Table 1, the relative potency of FDA was compared to other uterotonins. The Emax produced following administration of 2 mg/ml FDA was 2.45 ± 0.10 g. Meanwhile, the Emax produced following administration of 1 × 10⁻² M Ach, 7 IU oxytocin and 5 μg/ml PGF₂α were 2.98 ± 0.25, 3.51 ± 0.47 and 3.43 ± 0.19 g respectively.

Effect of oxodipine and EDTA on the Emax induced by 2 mg/ml FDA

In Figure 3, administration of oxodipine, a voltage-gated L-type Ca²⁺ channel antagonist into the bathing solution containing isolated uterine tissue pre-exposed to 2 mg/ml FDA resulted in the Emax to decrease by 88.5%. Meanwhile, administration of EDTA into this solution which resulted in depletion of extracellular Ca²⁺ caused the Emax to decrease by a greater percentage (96.8%). Lesser degree of inhibition by oxodipine and EDTA in isolated uterine tissue pre-exposed to oxytocin indicated that this effect of oxytocin was not solely dependent on the extracellular Ca²⁺.

Table 1 Relative potency of FDA as compared to other uterotonins

|          | Tension (g) |
|----------|-------------|
| FDA      | 2.45 ± 0.10 |
| Acetylcholine (Ach) | 2.98 ± 0.25 |
| Oxytocin | 3.51 ± 0.27 |
| Prostaglandin F₂α (PGF₂α) | 3.43 ± 0.19 |

FDA is 1.43 times less potent than oxytocin. This extract is also 1.40 and 1.21 times less potent than PGF₂α and Ach respectively. n = 6 per treatment group.

Effect of 2-APB and thapsigargin on the Emax induced by 2 mg/ml FDA

In Figure 4, administration of 2-APB, an IP₃R blocker into the bathing solution containing isolated uterine tissue pre-exposed to 2 mg/ml FDA did not cause any significant changes in the Emax produced. Meanwhile, administration of SERCA inhibitor, thapsigargin, resulted in 8.5% increase in the Emax as compared to FDA alone. 2-APB caused a significant decrease in the Emax in isolated uterine tissue pre-exposed to oxytocin, while thapsigargin administration resulted in the opposite effect.

Discussion

To the best of our knowledge, this study is the first to display uterotonic effect of Ficus deltoidea, which justifies the claim that this plant assists in uterine contraction. We have shown that FDA effect is mediated via muscarinic, oxytocin and PGF₂α receptors and is dependent on the extracellular Ca²⁺. These mechanisms were confirmed from inhibition of the maximum tension (Emax) produced by 2 mg/ml FDA following administration of the antagonists to these receptors and inhibitors to the Ca²⁺ channels. FDA is 1.43 times less potent than oxytocin, which is a gold standard uterotonin [15]. Apart from Ficus deltoidea, a few other Ficus species including Ficus exasperata [17,22] and Ficus asperifolia [1] were also reported to stimulate uterine contraction, suggesting that uterotonic effect is common to the Ficus species.

Our findings suggested that FDA-induced uterine contraction was mediated mainly via the oxytocin receptor as evidenced by the highest degree of inhibition of the
Emax by atosiban. Moderate inhibition of the Emax by THG113.31 suggested that FDA binding to PGF2α receptor produced moderate degree of contraction while the lowest inhibition by atropine suggested that FDA binding to the muscarinic receptor produced the least degree of contraction. The cumulative inhibitory effect observed following concomitant administration of atropine, THG113.31 and atosiban confirmed the involvement of all three receptors in mediating FDA-induced uterine contraction. The presence of muscarinic, oxytocin and PGF2α receptors in the uterus has been previously reported [23-25]. These receptors were reported to be up-regulated by E2 and in the late pregnancy particularly at term [26]. In view of this, high dose E2 administration

Figure 3 The effect of calcium channel blocker and extracellular calcium removal on FDA-induced uterine contraction. Representative image of isometric uterine contraction following administration of (a) 2 mg/ml FDA plus oxodipine, (b) oxytocin plus oxodipine, (c) 2 mg/ml FDA plus EDTA and (d) oxytocin plus EDTA while bar chart shows the Emax following oxodipine and EDTA administration as compared to the control. Contraction was almost abolished following EDTA administration in the isolated uteri pre-exposed to FDA. n = 6 (* p < 0.05).

Figure 4 The effect of IP3R blocker and SERCA inhibitor on FDA-induced uterine contraction. Representative image of isometric uterine contraction following administration of (a) oxytocin plus 2-APB, (b) FDA 2 mg/ml plus 2-APB, (c) oxytocin plus thapsigargin and (d) FDA 2 mg/ml plus thapsigargin while bar chart shows the Emax following oxytocin and FDA administration with and without the presence of 2-APB and thapsigargin. No significant difference was noted following 2-APB administration in the FDA treated group while thapsigargin caused a slight but significant increase in the Emax.
to the rats prior to the experiment can result in an increase in the number of these uterotonin receptors, potentiating the effect of FDA on uterine contraction.

There is a possibility that the greatest effect produced following FDA binding to the oxytocin receptor (as evidenced by the greatest inhibition of the Emax by atosiban) was due to high number of this receptor expression in the uterus. Meanwhile, lesser inhibition by THG113.31 and atropine suggested that the number of PGF2α and muscarinic receptors expressed was lower than the number of oxytocin receptor expression. Up-regulation of oxytocin receptor by E2 and at term [26,27] has been reported to increase uterine contraction through binding to the oxytocin receptor which is coupled to G protein α(i) potentiating the phospholipase C/Ca2+ dependent pathway, while activation of the muscarinic, oxytocin and PGF2α receptors may trigger the intracellular Ca2+ entry which would further enhance uterine smooth muscle contraction [49]. Our finding has shown that administration of thapsigargin, a SERCA inhibitor resulted in a slight but significant increase in the Emax induced by oxytocin and FDA. This effect could be due to the depletion of stored Ca2+ by thapsigargin which inhibit the re-uptake of cytosolic Ca2+ into the sarcoplasmic reticulum. The consistently high cytosolic Ca2+ will activate extracellular Ca2+ entry which would further enhance uterine smooth muscle contraction [50].

**Conclusion**

Using *in-vitro* model, our study has provided the first scientific evidence to support the claim that Ficus deltoidea stimulates uterine contraction. The active compound that is responsible in mediating this effect is currently...
unknown, although Ficus deltoidea has been reported to contain flavonoids isovitexin, vitexin [51], proanthocyanidins, flavan-3-ol monomer and flavones glycosides [52]. Phytochemical analyses further revealed the presence of tannins, tripterpenoids and phenols although alkaloids and steroids were not commonly found [10]. This \textit{in-vitro} study using isolated rodent’s uteri therefore provides preliminary evidence which could be used to further explore the \textit{in-vivo} effect of this plant compound on uterine contraction.

\textbf{Competing interests}

Authors have nothing to disclose.

\textbf{Authors' contributions}

NS is the project leader who planned this study, was involved in data interpretation and prepared the manuscript for publication. Meanwhile, VNA conducted all experiments. Both authors have read and approved the manuscript.

\textbf{Acknowledgement}

This study was supported by the UMRG grant RG404/12 HTM, University of Malaya, Kuala Lumpur, Malaysia. We would like to thank Dr Norhaniza Salleh and Ahmad Aminudin from the Institute of Biological Sciences, Faculty of Science, University of Malaya for her continuous support. We would also like to thank Dr Charlie Hindmarsh and Deirdre Hindmarsh from Bristol University, United Kingdom for proof-reading the manuscript.

\textbf{Received:} 14 June 2013 \textbf{Accepted:} 5 December 2013

\textbf{Published:} 14 December 2013

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http://www.biomedcentral.com/1472-6882/13/359

Cite this article as: Salleh and Ahmad: In-Vitro effect of Ficus deltoidea on the contraction of isolated rat’s uterus is mediated via multiple receptors binding and is dependent on extracellular calcium. BMC Complementary and Alternative Medicine 2013 13:359.