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Brénam Bitalatan
Laboratory of Physiology/Pharmacology, Department of Animal Physiology, Faculty of Sciences, University of Lomé, Togo

Tcha Pakoussi
Laboratory of Physiology/Pharmacology, Department of Animal Physiology, Faculty of Sciences, University of Lomé, Togo

Yendubé T Kantati
Laboratory of Physiology/Pharmacology, Department of Animal Physiology, Faculty of Sciences, University of Lomé, Togo

Gaston K Kodzovi
Laboratory of Physiology/Pharmacology, Department of Animal Physiology, Faculty of Sciences, University of Lomé, Togo

Bignoate Kombate
Laboratory of Physiology/Pharmacology, Department of Animal Physiology, Faculty of Sciences, University of Lomé, Togo

Enam A Motto
Laboratory of Physiology/Pharmacology, Department of Animal Physiology, Faculty of Sciences, University of Lomé, Togo

Kossi Metowogo
Laboratory of Physiology/Pharmacology, Department of Animal Physiology, Faculty of Sciences, University of Lomé, Togo

Povi L Evi
Laboratory of Physiology/Pharmacology, Department of Animal Physiology, Faculty of Sciences, University of Lomé, Togo

Aklesso P Mouzou
Laboratory of Physiology/Pharmacology, Department of Animal Physiology, Faculty of Sciences, University of Lomé, Togo

Kwashi E Gadegbeku
Laboratory of Physiology/Pharmacology, Department of Animal Physiology, Faculty of Sciences, University of Lomé, Togo

Correspondence:
Dr. Tcha Pakoussi
Department of Animal Physiology, Faculty of Sciences, University of Lomé, PoBox: 1515 Lomé, Togo
Email: unipak2000@gmail.com

Antioxidant, anti-inflammatory, and tocolytic effects of *Alchornea cordifolia* leaves extract: implications for the treatment of miscarriages

Brénam Bitalatan, Tcha Pakoussi, Yendubé T Kantati, Gaston K Kodzovi, Bignoate Kombate, Enam A Motto, Kossi Metowogo, Povi L Evi, Aklesso P Mouzou, Kwashi E Gadegbeku

ABSTRACT

Background: *Alchornea cordifolia* is traditionally used in West Africa to maintain pregnancy. However, no scientific study has proven its efficacy or safety in preventing miscarriage. **Objective:** The current study was undertaken to evaluate the tocolytic effect of the hydroethanolic extract of *A. cordifolia* leaves to provide scientific evidence for its use in treating pregnancy loss. **Materials and Methods:** Total flavonoids, total phenols and tannins were quantified in the hydro-ethanolic leaves extract of *A. cordifolia*. The antioxidant activity of the extract was evaluated by total antioxidant capacity, DPPH (2,2-diphenyl-1-picrylhydrazyl) scavenging activity, and iron-reducing capacity. Its anti-inflammatory activity was evaluated *in vitro* on rat erythrocytes using the membrane stabilization test. For tocolytic tests, myometrial flaps from Wistar rats were mounted in an organ bath containing Krebs-Henseleit physiological solution, and spontaneous contractions were recorded in the presence of the hydroethanolic extract of *A. cordifolia* leaves, oxytocin, misoprostol and indomethacin. **Results:** The *A. cordifolia* extract has a high antioxidant capacity of the *A. cordifolia* extract (243.39 ± 19.71 mg AA eq/g). It reduced the DPPH free radical (IC_{50} = 39.31 ± 0.69 µg/mL) compared to quercetin (IC_{50} = 22.27 ± 0.07 µg/mL). Compared to quercetin, the extract showed a strong iron-reducing capacity. The extract showed a strong anti-inflammatory activity by protecting erythrocyte membranes from hemolysis (IC_{50} = 424.6 ± 27.55 µg/mL) compared to aspirin (IC_{50} = 603.6 ± 193.8 µg/mL). The *A. cordifolia* extract (6.25 10^{-3} to 800 10^{-3} mg/mL) significantly reduced ($p < 0.05$) the tension and frequency of spontaneous myometrial contractions. In normal physiological saline, it reduced the uterotonic effect of oxytocin (10^{-5} IU/mL), and in calcium-free physiological saline, it inhibited the effect of oxytocin on the myometrium at high concentrations. The *A. cordifolia* extract and indomethacin (1 mg/mL) significantly reduced ($p < 0.05$) the effect of misoprostol (10^{-8} to 10^{-5} M) on the myometrium. **Conclusion:** The extract has a tocolytic effect and possesses antioxidant and anti-inflammatory activities. These results showed that the leaves of *A. cordifolia* plants can be used in the prevention of miscarriages.

Keywords: *Alchornea cordifolia*, Antioxidant Activity, Anti-Inflammatory Activity, Tocolytic Activity, Medicinal Plants, Miscarriage Prevention.

INTRODUCTION

Childbirth is the process by which a woman gives birth to a child. It occurs at the end of a pregnancy, which typically lasts between 37 and 40 weeks of amenorrhea. However, when it occurs before the 20th week of gestation, it is called a miscarriage [1]. A miscarriage is a spontaneous abortion without medical or mechanical intervention to terminate the pregnancy before fetal viability [2]. Many factors such as chromosomal abnormalities, structural abnormalities of the uterus, autoimmune disorders, endocrine disorders, and even poor lifestyle choices, contribute to pregnancy loss [3]. The therapeutic approach to preventing preterm births is the inhibition of preterm myometrial contractions using tocolytics such as calcium channel blockers, β-adrenergic agonists, or oxytocin receptor antagonists [4]. Several plants are used to stop threatened miscarriages, including *Semen cuscutae* [5], *Eleusine indica*, *Bombax buonopozense*, and *Portulaca oleracea* [6].

A survey conducted by the same authors showed that *A. cordifolia*, *Alstonia boonei*, and *Uvaria afzelii* are the most popular plants among pregnant women, who use them in the first and second trimesters to

to maintain their pregnancy. However, no scientific studies have yet been conducted to verify the effectiveness of these plants in maintaining pregnancy. *A. cordifolia* has hypoglycemic and antihyperglycemic effects [7]. The leaves of *A. cordifolia* restore reproductive dysfunction due to complications of diabetes in males [8]. These leaves also have antidiarrheal properties [9]. The leaves contain many bioactive compounds such as sterols, polyterpenes, phenols, flavonoids, catechins, and alkaloids [10]. These authors also showed that these leaves possess potent antioxidant properties and can be used in the treatment of diseases related to oxidative stress. Oxidative stress is implicated in miscarriages [11]. The roots of *A. cordifolia* possesses oxytocic properties [12]. However, no scientific studies have been conducted to evaluate the effect of *A. cordifolia* leaves on inhibiting myometrial contractions to demonstrate their potential use in treating miscarriages. This study aims to evaluate the tocolytic effect of the hydroethanolic extract of *A. cordifolia* leaves to demonstrate its role in preventing pregnancy loss.

MATERIAL AND METHODS

Plant material

The leaves of *A. cordifolia* were collected in August 2024 in the locality of Danyi N'Digbé (Assimé forest), a locality in the Kloto prefecture (Plateau Region) located 160 km northwest of Lomé. The botanical authentication of these leaves was established by the herbarium of the Laboratory of Botany and Plant Ecology of the Faculty of Sciences of the University of Lomé, where a reference specimen was deposited under the number TOGO03023. After harvesting, the leaves were washed with tap water, dried under air conditioning (20 °C) for two weeks in the dark, and then finely chopped.

Animals

The experiments involved young Wistar strain rats that had not yet given birth, weighing between 120 g and 160 g. The animals were raised in the animal facility of the Department of Animal Physiology at the University of Lomé. They had free access to water and food and were subjected to a 12 h light/12 h dark cycle. The experiments on these animals were conducted following the recommendations of the ethics committee of the Laboratory of Physiology/Pharmacology at the University of Lomé (Ref: 001/2012/CB-FDS-UL).

Experimental device

The absorbance of the different solutions for the antioxidant and anti-inflammatory tests was measured using a spectrophotometer (Genesis 20; Thermo Fisher Scientific, USA).

Recording uterine smooth muscle contractions was made possible using a device consisting of a 25 mL organ bath equipped with a tension sensor that transmits tension variations to the same module (ADInstruments, USA) serving as an interface and coupled to a microcomputer controlled by LabChart 8 software.

Chemicals and Reagents

Gallic acid and ascorbic acid were provided by Sigma-Aldrich (USA), indomethacin by Abbott (France), and oxytocin and misoprostol by GLP Pharma Standards (India). Quercetin and aspirin were provided by LKT Laboratories (USA). All chemicals were prepared on the day of the experiment.

Hydroethanolic extract preparation

Finely chopped leaves of *A. cordifolia* (200 g) were macerated in a mixture of equal volumes of ethanol and distilled water for 72 h with intermittent stirring at room temperature. The solvent was changed once, and the resulting macerate was filtered first through absorbent cotton and then through filter paper. The filtrate was evaporated under vacuum at 45 °C using a rotary evaporator (G1 Heildof, Germany) and then freeze-dried using a freeze dryer (Cryotec, France). The extract was obtained as brownish crystals with a yield of 25% and is soluble in water.

Quantification of phytochemical compounds

Quantification of total flavonoids

This was performed according to the method described by Zikpi *et al* [13]. The hydro-ethanolic extract and rutin were dissolved in 95° ethanol. A volume of 1 mL of aluminum trichloride (2%) was added to 1 mL of rutin solution (5, 25, 50, 75, 100, 150, or 200 µg/mL) and used as a standard. The same thing was done with the hydro-ethanolic extract instead of the rutin solution. The mixture was incubated at room temperature (25 ± 2 °C) for 10 min. A blank was prepared from aluminium trichloride and 95° ethanol. Absorbance was measured at 415 nm against a blank. Total flavonoids were expressed as mg rutin equivalents, with n = 3.

Quantification of total phenols and tannins

This was performed according to the method described by Agalatossi *et al* [14] with a slight modification. To 500 µL of the extract (1 mg/mL), 10 mg of polyvinylpolypyrrolidone (PVPP) and methanol were added. The resulting mixture was homogenized using a vortex mixer and incubated on ice for 30 min. After centrifugation, 200 µL of the supernatant were taken for analysis using the Folin-Ciocalteu reagent. The blank was prepared with 1 mL of methanol instead of the extract. Next, 200 µL of the extract solution (1 mg/mL), or 200 µL of gallic acid solution (25, 50, 100, 150, 200 µg/mL), or 200 µL of the extract and PVPP mixture, were added to 200 µL of the 10% Folin-Ciocalteu reagent. After 15 min of incubation at room temperature, 800 µL of sodium carbonate solution (700 mM) was added to the mixture. The optical density was read at 765 nm. The total phenol content was expressed as mg gallic acid equivalent/g of extract.

Antioxidant activity

Total antioxidant capacity

This was determined according to the method described by Atchou *et al* [15]. To 0.3 mL of different concentrations (25, 50, 75, 100, 150, 200, 250 µg/L) of ascorbic acid or to 0.3 mL of the extract solution (1 mg/mL) prepared with methanol, 3 mL of the prepared reagent (0.6 M sulfuric acid; 28 mM sodium phosphate; and 4 mM ammonium molybdate) was added. To a volume of 100 mL of solution, 494 mg of ammonium molybdate were added to 1003 mg of disodium sodium phosphate. After complete dissolution, 3.33 mL of sulfuric acid were added before adjusting the final volume to 100 mL. The absorbance of the reaction medium was read at 695 nm against a blank (methanol) after incubation at 95 °C for 90 min (n = 3). The antioxidant capacity was expressed as mg of ascorbic acid equivalent/g of extract.

DPPH (2,2-diphenyl-1-picrylhydrazyl) scavenging activity

This was determined according to the method described by Kantati *et al.* [16]. A DPPH solution was prepared by dissolving 3.9 mg of DPPH in 100 mL of methanol. To a volume of 1500 mL of the DPPH solution in dry tubes, 250 µL of methanol (blank) or 250 µL of the methanolic extract solution (12.5, 25, 50, 100, 200, and 500 µg/mL) was added. Quercetin at different concentrations (12.5, 25, 50, 100, 200, and 500 µg/mL) was used as a reference. Absorbance values were measured at 517 nm after 10 min of incubation. The results were presented as percentages of inhibition, and the IC_{50} values were determined.

Determination of the iron-reducing power of the extract

The iron-reducing antioxidant power (FRAP) of the extract was determined according to the method described by Kantati *et al* [17].

The FRAP reagent was prepared by mixing 300 mM sodium acetate buffer (pH 3.6), 10 mM TPTZ (tripiryridyltriazine) solution, and 20 mM $FeCl_3 \cdot 6H_2O$ solution in a 10:1:1 volume ratio. A 100 µL volume of different concentrations of *A. cordifolia* (12.5, 25, 50, 100, 200, 500, and 1000 µg/ml) was then added to 3 mL of the FRAP reagent, and the reaction mixture was incubated at 37 °C for 30 min. Quercetin was used as the reference antioxidant. The absorbance of the mixture was measured at 593 nm after 4 min of reaction. The experiment was carried out in triplicate (n = 3).

***In vitro* anti-inflammatory activity: membrane stabilization test**

The anti-inflammatory activity of *A. cordifolia* extract was evaluated according to the method described by Kpemissi *et al* [18]. Rats were anesthetized with ether, and blood was collected from the retro-orbital sinus of the eye into heparinized tubes. Erythrocytes were separated from the plasma and the buffy coat by centrifugation at 1500 rpm for 10 min and washed three times with the same volume of normal saline (0.9% NaCl). The resulting erythrocyte pellet was then resuspended in saline, and a 5% suspension was prepared for testing. A volume of 1 mL of *A. cordifolia* extract (prepared in normal saline solution) at different concentrations (25; 50; 100; 200; 500 and 1000 µg/mL) and 2 mL of hypo-saline solution (0.36%) were added to 1 mL of erythrocytes in suspension. Aspirin was used as the reference drug and treated similarly to the extract. Samples were kept in a water bath at 56 °C for 30 min. After cooling, the samples were centrifuged at 2500 rpm for 5 min. The absorbance of the supernatant was read at 560 nm. The assay was repeated three times for each concentration. 0.9% NaCl was used as a control. Membrane stabilization was expressed as a percentage of inhibition of erythrocyte hemolysis.

Tocolytic effect

Animal preparation and organ harvesting

Female rats were sacrificed by cervical dislocation under ether. The central portion of the uterine horns was harvested, cleaned of adhesions, and cut longitudinally into 0.5 cm x 0.3 cm flaps. These flaps were then placed in a 25 ml organ bath containing Krebs-Henseleit physiological saline solution with the following composition (mM): NaCl 118; KCl 4.7; $CaCl_2$ 2.5; KH_2PO_4 2.5; $MgSO_4$ 1.2; $NaHCO_3$ 25; glucose 11. The organ was fixed longitudinally in the organ tank with a wire and preloaded with 0.2 g. It was then continuously oxygenated and maintained at a temperature of 37 °C (pH 7.4).

Effect of A. cordifolia on spontaneous myometrial contractions

A myometrial flap was placed in an organ bath containing Krebs-Henseleit solution. It was left for approximately 45 min, during which time it was washed three times to restore equilibrium. After equilibration and stabilization, spontaneous contractions were recorded in the absence or in the presence of the extract.

Effect of A. cordifolia on oxytocin induced myometrial contractions in normal physiological saline

After stabilization of spontaneous myometrial contractions, oxytocin (Syntocinon®) was added to the Krebs-Henseleit physiological saline solution before the cumulative addition, 10 min later, of different volumes of extract. Spontaneous myometrial contractions were recorded in the presence of oxytocin followed by the extract.

Effect of A. cordifolia on oxytocin induced myometrial contractions in a calcium-free physiological solution

As before, after stabilization of spontaneous myometrial contractions, the Krebs-Henseleit physiological solution was replaced with a calcium-free solution. Then, oxytocin (Syntocinon®) was added to the organ bath. Ten minutes later, a single volume of extract was added. Spontaneous myometrial contractions were recorded in the presence of oxytocin followed by the extract.

Effect of A. cordifolia on prostaglandin pathway

After stabilization of spontaneous myometrial contractions, the extract was added to the organ bath before, 10 min later, misoprostol. Spontaneous myometrial contractions were recorded in the presence of the extract followed by misoprostol.

Similarly, the myometrium was incubated in indomethacin before, 10 min later, misoprostol added. Spontaneous myometrial contractions were recorded in the presence of indomethacin followed by misoprostol.

Statistical Analysis

Results were expressed as mean ± standard error. They were processed using GraphPad Prism 8.4.3 software (GraphPad Software Inc., California), which was also used to construct the histograms and curves. Analysis of variance (ANOVA) followed by Tukey's multiple comparison test was used to compare means and determine the significance of differences between treatments. Differences were considered significant when the p-value was < 0.05.

RESULTS

PHYTOCHEMICAL TESTS

Quantification of total flavonoids, total phenols and tannins

The *A. cordifolia* leaves extract contains total flavonoids, total phenols and tannins (Table 1).

Table 1: Concentration of total flavonoids, total phenols and tannins in the hydroethanolic extract of *A. cordifolia* leaves

Phytochemical compounds	Concentration
Total phenols	162.07 ± 3.65 mg GAE/g
Tannins	151.67 ± 2.89 mg GAE/g
Flavonoids	102.55 ± 0.74 mg RE/g

Values were expressed as mean ± SEM (n = 3)
Polyphenols and tannins are expressed as mg gallic acid equivalent/g of extract (mg GAE/g). Flavonoids are expressed as mg rutin equivalent/g of extract (mg RE/g)

PHARMACOLOGICAL TESTS

Antioxidant Tests

DPPH radical scavenging Test

The IC_{50} values of the extract and quercetin (Table 2) were showed that the *A. cordifolia* extract has a strong capacity to scavenge DPPH free radicals

Table 2: Antiradical activity of quercetin and *A. cordifolia*

IC_{50} (µg/mL)	Quercetin	*A. cordifolia*
	22.27 ± 0.07	39.31 ± 0.69

IC_{50}: inhibitory concentration 50, presented as mean ± SEM (n = 3)

Test of the reducing antioxidant power of iron

The absorbance of the extract increased with concentration, indicating an increase in reducing power. The extract has a higher reducing power than quercetin (Figure 1).

Total antioxidant capacity

The capacity of all the antioxidant compounds presents in the extract, as an ascorbic acid equivalent, determined from the ascorbic acid calibration curve, is 243.39 ± 19.71 mg AA eq/g of extract. This value demonstrates that the *A. cordifolia* extract possesses antioxidant capacity.

***In vitro* anti-inflammatory test**

The IC50 values of the extract and aspirin were 424.6 ± 27.55 µg/mL and 603.6 ± 193.8 µg/mL respectively (Figure 2). The extract stabilized the erythrocyte membrane better than aspirin.

A. cordifolia extract exhibits anti-inflammatory activity by protecting the erythrocyte membrane from hemolysis.

TOCOLYTIC EFFECT

Effect of *A. cordifolia* on spontaneous myometrial contractions

The hydroethanolic extract of *A. cordifolia* induced a reduction in spontaneous uterine muscle contractions (Figure 3A). The tension of spontaneous myometrial contractions was significantly reduced ($p < 0.05$) starting at a concentration of 100 10^{-3} mg/mL (Figure 3B). The frequency of spontaneous contractions was also significantly reduced ($p < 0.05$) starting at a concentration of 50 10^{-3} mg/mL (Figure 3C). The extract has utero-relaxing effect.

Effect of *A. cordifolia* on oxytocin induced myometrial contractions in normal physiological solution

Oxytocin (5 10^{-5} IU/mL) induced an increase in myometrial contractions which were reduced when the extract was added (Figure 4A). The extract was reduced both the tension and the frequency of uterine contractions in the presence of oxytocin (Figures 4B and 4C).

In the presence of oxytocin (5 10^{-5} IU/mL), the IC_{50} of the extract (0,732 ± 0,04 mg/mL) was more than 1.08 times higher than that of the extract alone (0,679 ± 0,28 mg/mL) (Figure 4D).

The hydroethanolic extract of *A. cordifolia* reduced the effects of oxytocin on uterine smooth muscle. It is anti-oxytocic.

Effect of *A. cordifolia* on oxytocin induced myometrial contractions in calcium-free solution

Spontaneous myometrial contractions were inhibited in a calcium-free medium. In this medium, oxytocin at 5 10^{-5} IU/mL failed to induce the resumption of uterine contractions. However, at a concentration of 10^{-4} IU/mL, it induced a resumption of uterine smooth muscle contractions (Figure 5A). The extract at a concentration of 100 10^{-3} mg/mL significantly ($p < 0.01$) reduced this effect of oxytocin on uterine smooth muscle incubated in a calcium-free medium (Figure 5B), and completely inhibited the effect at a concentration of 800 10^{-3} mg/mL (Figure 5C). The tension of spontaneous uterine smooth muscle contractions was significantly ($p < 0.01$) reduced (Figure 5D).

Effect of A. cordifolia on the prostaglandin pathway

Uterine smooth muscle contractions induced by misoprostol in the presence of A. cordifolia

Spontaneous uterine smooth muscle contractions were increased in the presence of misoprostol (Figure 6A). The tension of contractions increased at concentrations of 10^{-8} M and 10^{-7} M and decreased at concentrations of 10^{-6} M and 10^{-5} M (Figure 6C). Misoprostol resulted in a significant increase ($p < 0.05$) in spontaneous myometrial contractions only at 10^{-7} M in the presence of the extract (AC800) (Figures 6B and 6C)

The hydro-ethanolic extract of *A. cordifolia* reduced the effects of misoprostol on uterine smooth muscle.

Uterine smooth muscle contractions induced by misoprostol in the presence of indomethacin

Spontaneous myometrial contractions were inhibited by indomethacin (1 mg/mL). In the presence of indomethacin, misoprostol no longer induced an increase in myometrial contractions (Figure 7).

Indomethacin inhibited the effect of misoprostol on uterine smooth muscle.

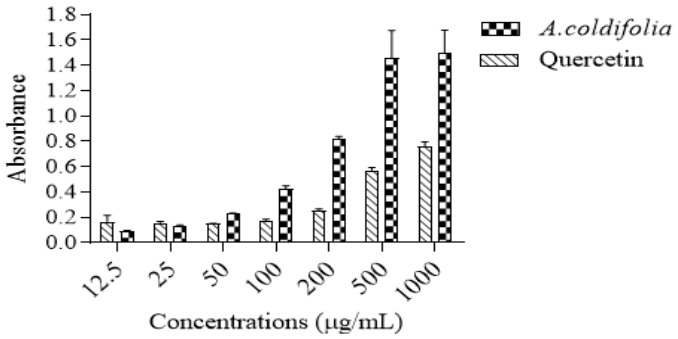


Figure 1: Reducing power of the *A. cordifolia* extract
Absorbance histograms of the extract or quercetin mixture with the FRAP solution, expressing their iron-reducing power (n = 3)

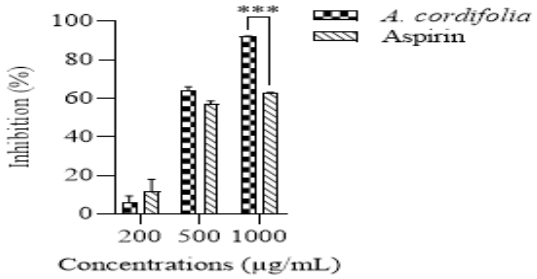


Figure 2: Erythrocyte membrane stabilization
Percentage of erythrocyte hemolysis inhibition as a function of the concentrations of the hydro-ethanolic extract of *A. cordifolia* and the reference drug (Aspirin). $^{***}p < 0.001$ (n = 3); ANOVA followed by Tukey's test

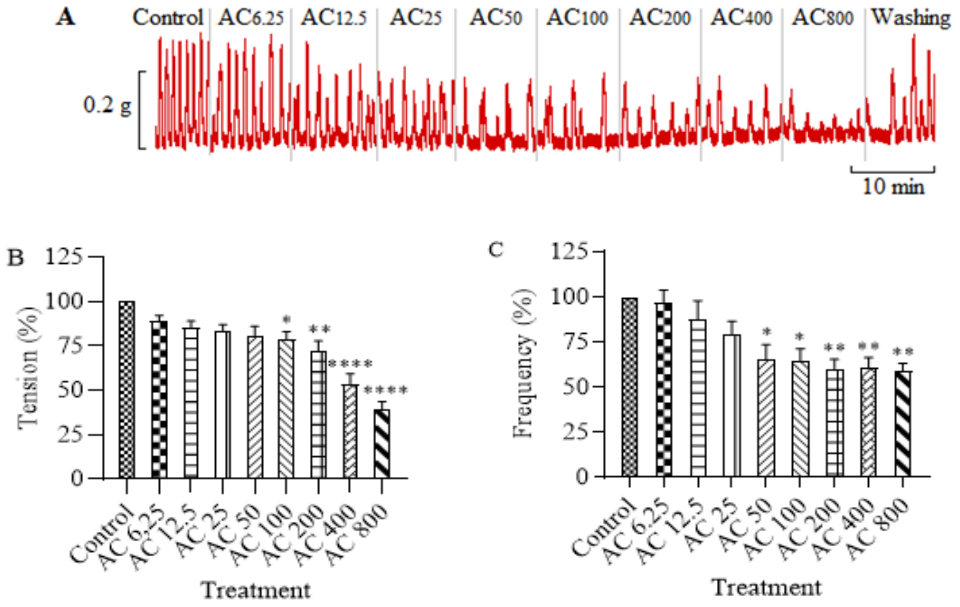
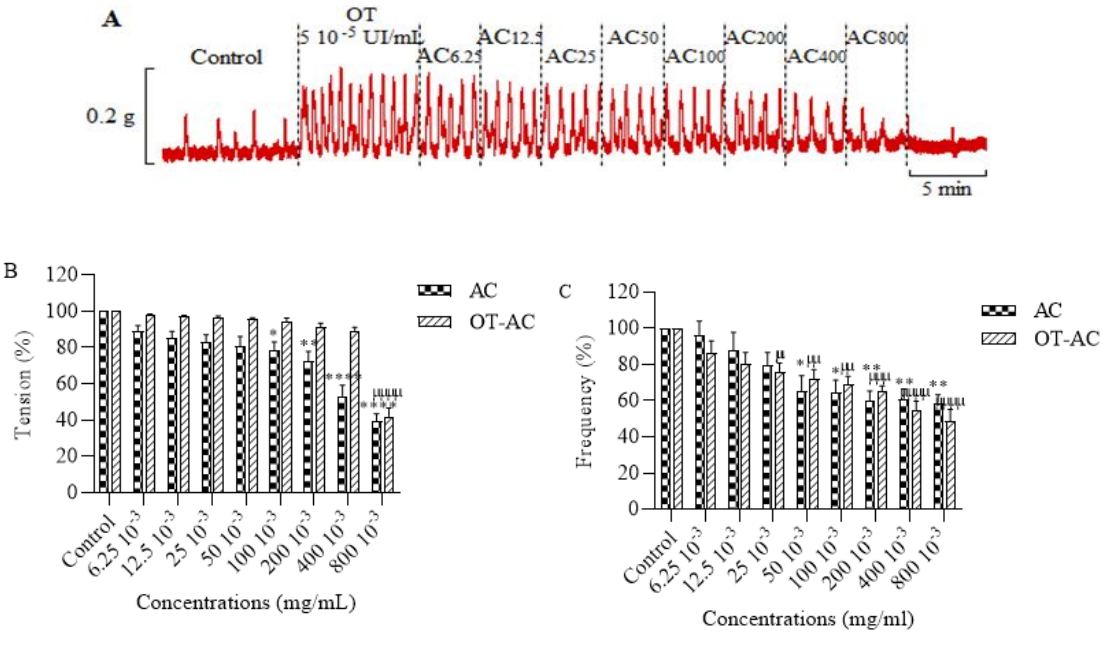


Figure 3: Effect of *A. cordifolia* on spontaneous uterine muscle contractions
Spontaneous rat myometrial contractions in the presence of *A. cordifolia* extract (A). Tension (B) and frequency (C) of spontaneous rat myometrial contractions in the absence (control) and presence of the extract. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ (n = 6). Values were expressed as mean percentages ± SEM. One-way ANOVA followed by Tukey's test.
AC6.25: *A. cordifolia* at 6.25 10^{-3} mg/mL; AC12.5: *A. cordifolia* at 12.5 10^{-3} mg/mL; AC25: *A. cordifolia* at 25 10^{-3} mg/mL; AC50: *A. cordifolia* at 50 10^{-3} mg/mL; AC100: *A. cordifolia* at 100 10^{-3} mg/mL; AC200: *A. cordifolia* at 200 10^{-3} mg/mL; AC400: *A. cordifolia* at 400 10^{-3} mg/mL; AC800: *A. cordifolia* at 800 10^{-3} mg/mL.



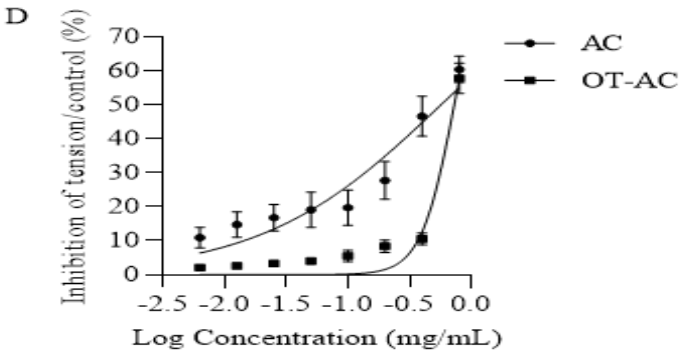


Figure 4: Effect of the hydroethanolic extract of *A. cordifolia* on oxytocin induced uterine smooth muscle contractions in normal physiological solution
Spontaneous myometrial contractions induced by *A. cordifolia* in the presence of oxytocin (5 10^{-5} IU/mL) (A).
Tension (B) and frequency (C) of spontaneous myometrial contractions induced by the extract alone (AC) and then induced by the extract in the presence of 5 10^{-5} IU/mL of oxytocin (OT-AC). $^{*}p < 0.05$; $^{**}p < 0.01$; $^{****}p < 0.0001$; $^{\#}p < 0.05$; $^{\#\#}p < 0.01$; $^{\#\#\#}p < 0.001$; $^{\#\#\#\#}p < 0.0001$; n = 6 ("*"; "**" "****" comparison with the control of extract alone; "#"; "##"; "###"; "####" comparison with the control of the extract in the presence of oxytocin). Values were expressed as mean percentages ± SEM. One-way ANOVA followed by Tukey's test.
Normalized logarithmic curve (D) of the tension of spontaneous myometrial contractions induced by the extract alone (AC) and then induced by the extract in the presence of 5 10^{-5} IU/mL of oxytocin (OT-AC)

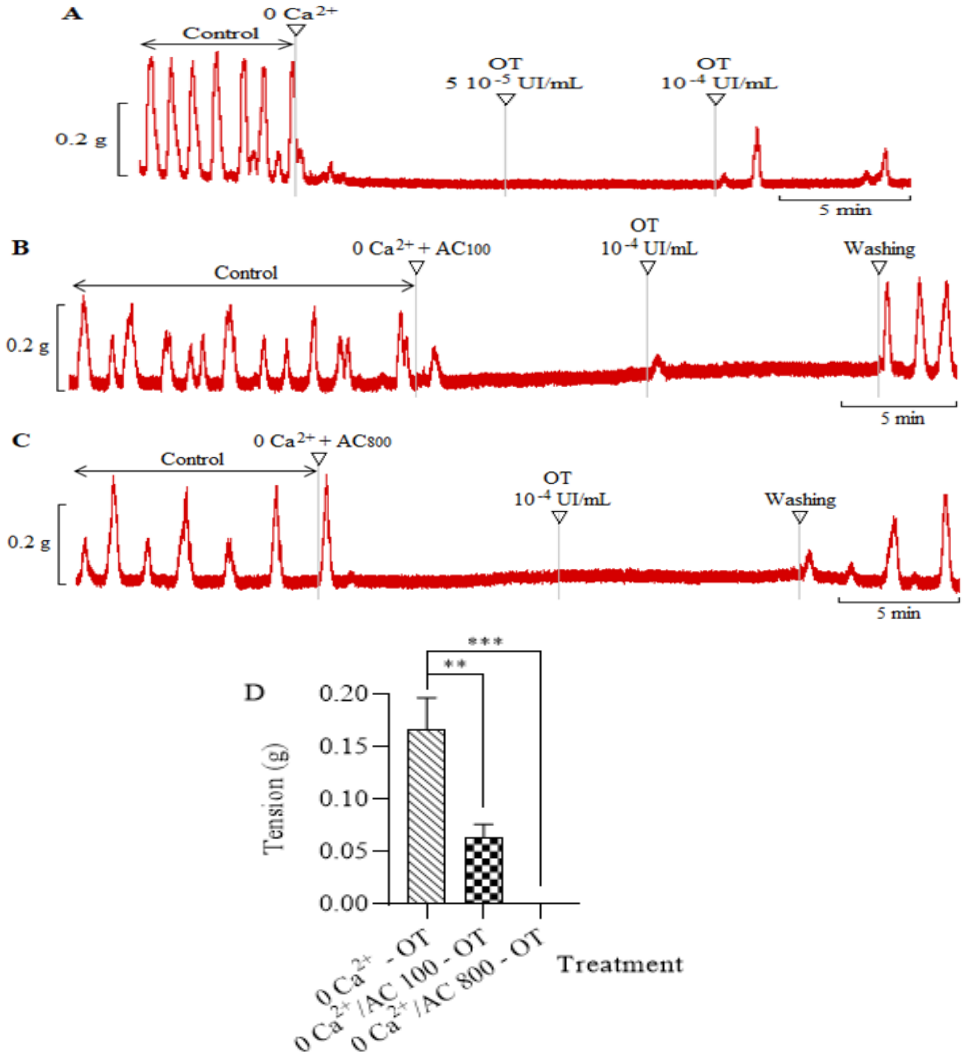


Figure 5: Effect of the hydroethanolic extract of *A. cordifolia* on oxytocin induced myometrial contractions in calcium-free medium
Spontaneous myometrial contractions induced by oxytocin in a calcium-free medium (A); by oxytocin (10^{-4} IU/mL) in a calcium-free medium containing the extract at 100 10^{-3} mg/mL (B) and by oxytocin (10^{-4} IU/mL) in a calcium-free medium containing the extract at 800 10^{-3} mg/mL (C). Tension of spontaneous myometrial contractions (D) induced by oxytocin (10^{-4} IU/mL) in a calcium-free medium, a calcium-free medium containing extract at 100 10^{-3} mg/mL, or a calcium-free medium containing extract at 800 10^{-3} mg/mL.
$0Ca^{2+}$: calcium-free medium; AC100: *A. cordifolia* at 100 10^{-3} mg/mL; AC800: *A. cordifolia* at 800 10^{-3} mg/mL. $^{**}p < 0.01$; $^{***}p < 0.001$ (n = 5). Values were expressed as mean percentages ± ESM. One-way ANOVA followed by Tukey's test

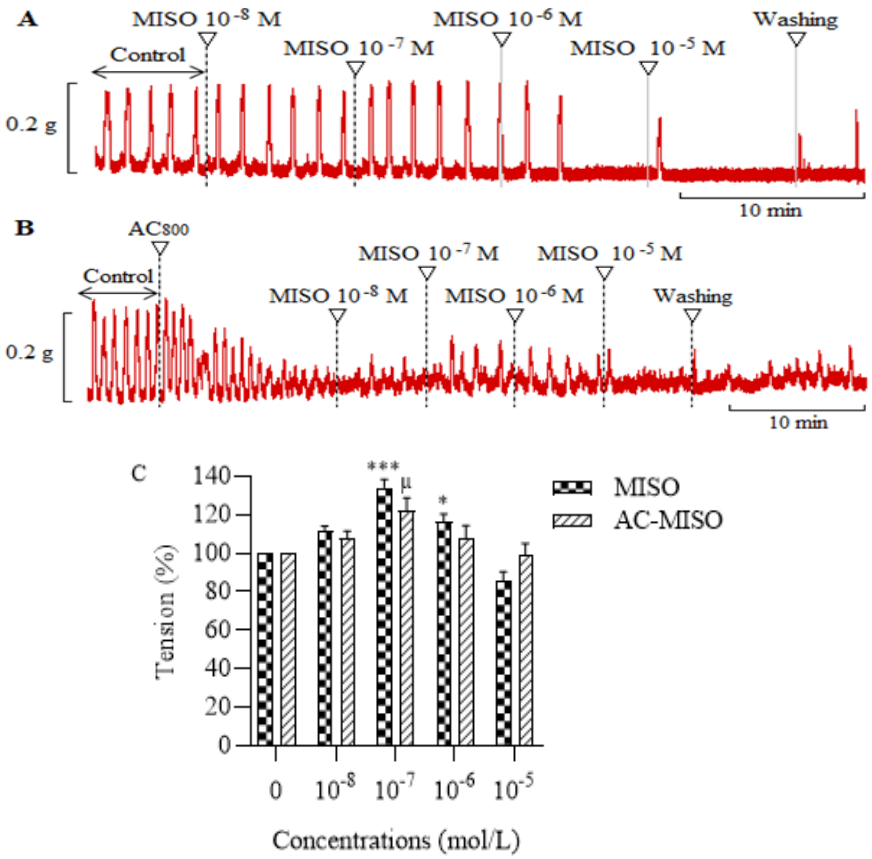


Figure 6: Effect of *A. cordifolia* on misoprostol induced uterine smooth muscle contractions
Spontaneous myometrial contractions induced by misoprostol alone (10^{-8} M; 10^{-7} M; 10^{-6} M; 10^{-5} M) (A) and by misoprostol in the presence of the extract at 800 10^{-3} mg/mL (B). Tension of spontaneous myometrial contractions (C) induced by misoprostol alone and by misoprostol in the presence of the extract at 800 10^{-3} mg/mL. MISO: misoprostol; AC800: *A. cordifolia* at 800 10^{-3} mg/mL; AC-MISO: misoprostol in the presence of the *A. cordifolia*. $^{***}p < 0.001$; $^{\mu}p < 0.05$; n = 5 ("**" comparison with the misoprostol control alone; "µ"" comparison with the misoprostol control in the presence of the extract). Values were expressed as mean percentages ± SEM. One-way ANOVA followed by Tukey's test

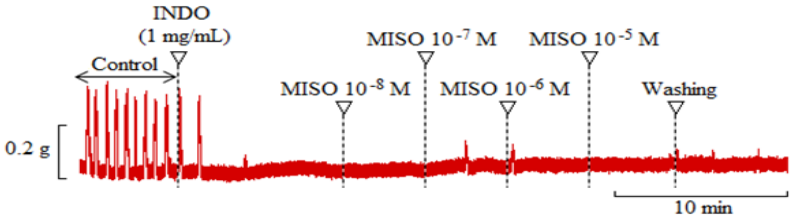


Figure 7: Effect of indomethacin on misoprostol induced uterine smooth muscle contractions
Spontaneous myometrial contractions induced by misoprostol (10^{-8} M; 10^{-7} M; 10^{-6} M; 10^{-5} M) in the presence of indomethacin (1 mg/mL). Arrows indicate the times of indomethacin or misoprostol addition or the time of washing

DISCUSSION

Structural abnormalities of the uterus are one of the factors contributing to spontaneous abortion or pregnancy loss [3]. Uterine hyperexcitability or hypertonia contributes to threatened miscarriage [19]. Progestins are often used in the treatment of miscarriages; however, studies have shown that progestins may be beneficial in women with a history of miscarriages, while their efficacy in women without a history remains uncertain [20,21]. The therapeutic approach to preventing preterm births is the inhibition of preterm myometrial contractions with tocolytics such as calcium channel blockers, β-adrenergic agonists, or oxytocin receptor antagonists [4]. Medicinal plants are particularly important in the treatment of recurrent miscarriages; and quercetin, a natural flavonoid polyphenol found in plants, has been recognized for its ability to alleviate these recurrent miscarriages [22]. In sub-Saharan Africa, several plants, known as "childbirth facilitators," are traditionally used to prevent miscarriages and premature births. These include *Eleusine indica*, *Bombax buonopozense*, and *Portulaca oleracea* [6]. According to these authors, *A. cordifolia*, *Alstonia boonei*, and *Uvaria afzelii* are the most popular among pregnant women. This study evaluated the uterine-relaxing effect of the hydro-ethanolic extract of *A. cordifolia* leaves, its antioxidant capacity, and its anti-inflammatory activity to establish its efficacy in treating threatened miscarriage.

The hydro-ethanolic extract of *A. cordifolia* leaves caused a reduction in the tension and frequency of uterine contractions. *A. cordifolia* leaves therefore have a uterine-relaxing effect. This result is consistent with the antioxidant activity of *A. cordifolia* leaves. Indeed, oxidative stress is implicated in miscarriages through its action on impaired placental vascularization, apoptosis in fetal and placental cells, and the exacerbation of inflammatory responses [11] Fujimaki *et al* [23] also showed that oxidative stress is involved in various pregnancy-related disorders, including recurrent miscarriages, preeclampsia, intrauterine growth restriction, preterm birth, and premature rupture of membranes. Based on our results regarding the antioxidant capacity of *A. cordifolia* leaves, the high antioxidant capacity of the *A. cordifolia* extract (243.39 ± 19.71 mg AA eq/g) indicates its strong potential to neutralize free radicals. The IC_{50} value of 99.285 ± 0.118 µg/mL obtained with the *A. cordifolia* shows that it moderately neutralizes the DPPH free radical. The high reducing power of iron compared to quercetin demonstrates the extract's high antioxidant capacity. In summary, the *A. cordifolia* extract has a strong antioxidant capacity. This result is consistent with that of Kone *et al* [10], who also showed that *A. cordifolia* leaves possess high antioxidant capacity and can be

used as a source of bioactive compounds in the prevention and treatment of diseases related to oxidative stress.

Reactive oxygen species are key signaling molecules that play an important role in the progression of inflammatory disorders [24]. According to these authors, M1 or classically activated macrophages produce excessive oxidative stress and secrete pro-inflammatory cytokines (IL-1, IL-6, and TNFα). Christiaens *et al* [25] showed that both full-term and preterm births are associated with the inflammatory process, characterized by both leukocyte infiltration and the production of pro-inflammatory cytokines by uterine tissues. To verify the anti-inflammatory effect of the *A. cordifolia* extract, we performed a membrane stabilization assay on erythrocytes. The results of this test revealed that both the extract and the reference drug (aspirin) protect erythrocytes against hemolysis during inflammation. The extract exhibited strong anti-inflammatory activity, with its IC_{50} (424.6 ± 27.55 µg/mL) being lower than that of aspirin (603.6 ± 193.8 µg/mL). The extract stabilized the erythrocyte membrane. This result is similar to that of Oruka *et al* [26], who showed that the aqueous extract of *A. cordifolia* increased erythrocyte membrane stabilization in a concentration-dependent manner.

The uterine-relaxing, antioxidant, and anti-inflammatory effects of *A. cordifolia* extract justify its use in the treatment and prevention of miscarriages.

A. cordifolia leaves contain flavonoids, phenols, and total tannins. These results corroborate those of Kone *et al* [10], who also identified terpenic compounds (sterols and polyterpenes), phenolic compounds (flavonoids and catechin tannins), and alkaloids in these leaves. Studies have shown the role of phenolic compounds in the antioxidant capacity of fruits and vegetables with a high correlation coefficient [27]. Flavonoids and phenolic glycosides have inhibitory effects on spontaneous uterine muscle contractions [28,29]. Novaković *et al* [30] and Habiburrahman *et al* [31] respectively demonstrated the tocolytic, uterine-relaxing effects and the role of a polyphenol (resveratrol) in preventing preterm birth. These chemical compounds exert their relaxing effect on uterine smooth muscle by decreasing intracellular calcium through several mechanisms: reducing prostaglandin E2 and F2α levels, stimulating calcium-dependent, ATP-dependent and then voltage-dependent potassium channels, and stimulating β-adrenergic receptors [31]. Commonly used tocolytics for preventing threatened preterm labor include calcium channel blockers, oxytocin receptor blockers, nitric oxide donors, β-adrenergic agonists and cyclooxygenase inhibitors [32,33]. The effect of the hydroethanolic extract of *A. cordifolia* leaves was evaluated on oxytocin-induced uterine contractions and on contractions induced by a prostaglandin E receptor agonist, and subsequently on calcium signaling.

The extract, only at high concentrations (800 10^{-3} mg/mL), reduced the effect of oxytocin on rat myometrium in normal physiological saline. In calcium-free physiological saline, the extract reduced the effect of oxytocin at a concentration of 100 10^{-3} mg/mL and inhibited this effect at a concentration of 800 10^{-3} mg/mL. It therefore has a tocolytic effect. The high concentration of the extract required to reduce the effect of oxytocin explains the increase of IC_{50} value. This tocolytic effect of the extract is likely due to its richness in bioactive phenolic compounds responsible for its antioxidant capacity. The tension of uterine contractions induced by the highest concentration of the extract alone is 60.43 ± 3.94%, while that of uterine contractions induced by the highest concentration of the extract in the presence of oxytocin is 57.85 ± 4.48%. On the one hand, the percentage of inhibition of uterine contraction tension induced by the highest concentration of the extract in the presence of oxytocin decreases slightly compared to that induced by the highest concentration of the extract alone. On the other hand, the concentration-effect curve of the extract in the presence of oxytocin shifts to the right compared to that of the extract alone. This suggests that the extract could act as an antagonist or modulator of oxytocin receptors or the calcium pathway. This result is consistent with that of Schiffmann and Gimpl [34], who showed that Mg^{2+} is a positive modulator of oxytocin receptors, with the dose-response curve of the oxytocin receptor antagonist in the presence of Mg^{2+} shifting to the right of that of the antagonist in the absence of Mg^{2+}, and identical Emax values.

Oxytocin binding to its membrane receptor, a Gαq protein-coupled receptor, activates phospholipase C [35,36]. Activation of phospholipase C leads to the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP2) with the formation of diacylglycerol and inositol 3-phosphate (IP3). IP3 activates the IP3 receptor and triggers the release of calcium from intracellular stores. The increase in intracellular calcium activates myosin light chain kinase, which phosphorylates myosin, subsequently leading to the contraction of myometrial cells [37,38]. Oxytocin also triggers calcium influx across the plasma membrane to increase intracellular calcium and initiate contraction [39]. Reducing the effect of oxytocin with the extract at high concentration in normal physiological saline demonstrates that the extract inhibits calcium influx into myometrial cells. Inhibiting the effect of oxytocin in a calcium-free medium in the presence of the extract shows that the extract prevents the release of calcium from intracellular stores by oxytocin. This result is consistent with that of Matsuki *et al* [40], who showed that, in a calcium-free medium, oxytocin stimulates the release of intracellular calcium from the sarcoplasmic reticulum to increase its cytosolic concentration.

Misoprostol, a synthetic analog of prostaglandin E, is used, like oxytocin, to induce safe and effective labor during premature rupture of membranes at term [41]. This study showed that the low concentrations of misoprostol used (10^{-8} M and 10^{-7} M) increased the tension of spontaneous myometrial contractions, while high concentrations (10^{-6} M and 10^{-5} M) reduced them. This result confirms that of Terry *et al* [42], who obtained a uterocontractile effect of misoprostol in rats and guinea pigs, with a peak at a concentration of 10^{-7} M. The same effect of misoprostol is observed in the human myometrium, with a biphasic effect [43]. Li *et al* [44] showed that prostaglandin E2 also has a biphasic effect in humans, with an increase in spontaneous myometrial contractions followed by relaxation. Misoprostol resulted in a significant increase in the tension of spontaneous myometrial contractions in rats. However, the tension obtained was not as strong. This result is similar to that obtained by Balki *et al* [45] with myometrial samples from women. The lower tension obtained with misoprostol is probably explained by the fact that it acts more on cervical dilation, membrane activation, and the coordination of contractions than on myometrial contraction, which is primarily stimulated by prostaglandin F2α [44]. The reduced effect of misoprostol in the presence of the extract is explained by an antagonistic effect on prostaglandin E receptors. The extract reduces the increase in intracellular calcium by blocking prostaglandin E receptors. In the presence of indomethacin (1 mg/mL), spontaneous contractions of the myometrium were suppressed. This result is similar to that of Sawdy *et al* [46], who also obtained suppression of spontaneous myometrial contractions with high concentrations of indomethacin through inhibition of calcium current. The high concentration of indomethacin used inhibits the effect of misoprostol on spontaneous myometrial contractions. Prostaglandin E2 induces myometrial contraction by increasing calcium levels through membrane calcium channels, following stimulation of EP1 receptors, and by inhibiting adenylate cyclase and thus reducing cAMP, following stimulation of EP3 receptors [47]. Indomethacin therefore inhibits the increase in intracellular calcium, preventing rat myometrial contractions, consistent with the work of Sawdy *et al* [46].

CONCLUSION

Herbal medicine strives to overcome numerous diseases, pathologies, and obstetric complications that devastate populations, especially in rural areas. Miscarriage is one such obstetric complication that has been the subject of several ethnopharmacological studies. *A. cordifolia*, a plant whose roots possess oxytocic properties, was the focus of our study. Indeed, the hydro-ethanolic extract of its leaves demonstrated an anti-oxytocic effect by reducing spontaneous myometrial contractions and oxytocin-induced myometrial

contractions in both normal physiological saline and calcium-free saline solutions. Misoprostol-induced myometrial contractions were also reduced in the presence of the hydro-ethanolic extract, as well as in the presence of indomethacin. All these actions of *A. cordifolia* leaves demonstrate their tocolytic properties and potential use in preventing miscarriages. This property of the hydro-ethanolic extract of *A. cordifolia* leaves is likely due to its strong antioxidant capacity, anti-inflammatory activity, and richness in phenolic compounds. However, further studies on pregnant rats receiving the leaf extract and subjected to experimental miscarriage conditions, *in vivo* anti-inflammatory tests, other *in vitro* tests, and investigations of β-adrenergic receptors and other mechanisms of action of the extract will be necessary.

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Author Contributions

BB and TP conceived the project, conducted the literature review, performed the data analysis, and wrote the manuscript. BB, TP, and GKK carried out the research on tocolytic effects. BB, YTK, and EAM conducted the research on antioxidant assays. BB and BK conducted the research on anti-inflammatory assays. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available and will be made available upon request.

Use of AI in Drafting of Manuscript

The authors declare that they have not used any generative AI/AI-assisted technologies in the writing of this manuscript.

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ORCID ID

Brénam Bitalatan: https://orcid.org/0009-0008-5920-1911

Tcha Pakoussi: https://orcid.org/0000-0003-1994-2359

Yendubé T Kantati: https://orcid.org/0000-0002-7515-494X

Gaston Kodzo Kodzovi: https://orcid.org/0009-0004-2960-8658

Bignoate Kombate: https://orcid.org/0000-0001-9340-022X

Enam Aku Motto: https://orcid.org/0000-0002-1360-2989

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