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Uterine contractility of plants used to facilitate childbirth in Nigerian ethnomedicine

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ABSTRACT

Ethnopharmacological relevance: Pregnant women in Nigeria use plant preparations to facilitate childbirth and to reduce associated pain. The rationale for this is not known and requires pharmacological validation.

Aim of study: Obtain primary information regarding the traditional use of plants and analyze their uterine contractility at cellular level.

Materials and methods: Semi-structured, open interviews using questionnaires of traditional healthcare professionals and other informants triggered the collection and identification of medicinal plant species. The relative traditional importance of each medicinal plant was determined by its use-mention index. Extracts of these plants were analyzed for their uterotonic properties on an *in vitro* human uterine cell collagen model.

Result: The plants *Calotropis procera*, *Commelina africana*, *Duranta repens*, *Hyptis suaveolens*, *Ocimum gratissimum*, *Saba comorensis*, *Sclerocarya birrea*, *Sida corymbosa* and *Vernonia amygdalina* were documented and characterized. Aqueous extracts from these nine plants induced significant sustained increases in human myometrial smooth muscle cell contractility, with varying efficiencies, depending upon time and dose of exposure.

Conclusion: The folkloric use of several plant species during childbirth in Nigeria has been validated. Seven plants were for the first time characterized to have contractile properties on uterine myometrial cells. The results serve as ideal starting points in the search for safe, longer lasting, effective and tolerable uterotonic drug leads.

1. Introduction

Traditional cultures often rely on the beneficial effects of herbal remedies during pregnancy, birth and postpartum care. The knowledge and the correct use of these natural medicines has been acquired and improved over many generations. It is estimated that 85% of the population in developing countries depend mainly on traditional healthcare systems (Center for Gender and Social Policy Studies 2012). The majority of Nigerians in the rural areas at some stage in their life turn to traditional healthcare as a result of accessibility, availability, affordability and inherent trust in this method (Ogbe et al., 2009). During pregnancy and childbirth traditional medicine relies on the use of certain herbs for their beneficial effects to tone the uterus muscle, induce labor, in the removal of retained placenta and management of postpartum bleeding (Gruber and O'Brien, 2011). The state of maternal health in Nigeria is poor and can be attributed to inadequate access to reproductive health services, poverty and in some areas cultural resistance that affects in particular women of rural areas with low access to primary healthcare (Central Intelligence Agency, 2012). For instance, in the year 2000 the maternal mortality in Nigeria was estimated to ~1% (United Nations Development Report, 2008; World Health Organisation, 2007) and Nigeria is one of 6 countries which together account for nearly half (49%) of all maternal deaths worldwide (Hogan et al., 2010). This contrasts sharply with other developing economies such as China, Egypt or Mexico, which had a maternal mortality rate ranging between 0.05 and 0.08% (World Health Organisation, 2007). Documentation and standardization of medical plants and their correct use will improve reproductive health of local

Abbreviations: UM, use-mentions; hTERT-HM, human uterine myometrial smooth muscle cells

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populations in Nigeria. At least as importantly, scientific validation of these traditional remedies is a crucial step in the discovery of natural drugs for the treatment of childbirth-related complications. Currently available therapies to induce or delay labor often have harmful side effects for mother and baby (Gruber and O'Brien, 2011; Plested and Bernal, 2001). Hence, there is a great need for potent, selective and non-toxic therapeutic agents that regulate uterine muscle action, both as suppressors or as stimulators (Gruber and O'Brien, 2011).

In line with the on-going effort at conserving important medicinal plants in Nigeria (Sonibare and Gbile, 2008; Sonibare et al., 2009), the present study has been designed to document and analyze some of the most frequently used plants of Nigeria to manage and facilitate the childbirth process. Following interviews of traditional healthcare professionals, we aim to determine the uterotonic properties of aqueous plant extracts, as claimed by the local users, at the cellular level, on an *in vitro* human uterine collagen model. Ethnobotanical survey and pharmacological validation is an important approach in the identification, selection and development of therapeutic agents from medicinal plants and this targeted approach often yields potentially useful compounds (Cragg et al., 1997).

2. Materials and methods

2.1. Study location and interview procedure

The study was conducted in Sokoto (13°04′N, 5°14′E) - Sokoto State (North), Kubwa (9°8′50″N, 7°21′4″E) and Wuse II (9°4′27″N, 7°27′53″E) - Abuja (North Central and Federal Capital Territory) and Egbetua quarter, Ososo (07°25′N, 06°16′E) - Edo State (South). Locations were randomly selected with special considerations for localities with very low access to primary healthcare services. Professional herbalists or traditional medical healers (who also function as birth attendants), local midwives (local birth attendants), farmers or local traders, teachers and artisans were interviewed orally using open, semi-structured questionnaires. The survey included questions about the usage of plants to aid and to facilitate the birth process, to reduce the time and associated pain of labor, prevent retained placenta and manage postpartum complications (see Appendix A).

2.2. Ethnopharmacological data analysis

The questionnaire data were analyzed according to the use-mentions (UM) principle as introduced by Andrade-Cetto (2009), Andrade-Cetto and Heinrich (2011). The UM has been defined as "the number of mentions for one plant given by all informants for a specific disease". To compare our survey data (see Appendix B) for all plants with the same use, we introduced a 'use-mention-index' (UM_I), which we defined as the number of mentions for one plant for a defined use category, divided by the total number of informants interviewed for the use category (n_u): $UM_I = UM/n_u$

For our analysis, we classified the traditional uses into three main categories, *i.e.*, plants used during pregnancy, at birth and for postpartum care. These main categories were further divided into eight sub-categories (see Appendix B).

2.3. Plant collection and preparation of extracts

Plants were collected according to the informants' instructions and under protection of the biodiversity rights of indigenous people and the local government. Samples were identified according to the Angiosperm Phylogeny Group III system, dried and deposited in the Forest Herbarium Ibadan (FHI) or the Department of Biological Sciences Herbarium, Ahmadu Bello University, Zaria (ABU). The dried and powdered plant material was extracted with methanol:dichloromethane (1:1; v/v) for 12–16 h under continuous agitation at 25 °C. After adding 0.5 volumes of ddH_2O to the filtered supernatant the aqueous phase was extracted on C_{18} solid-phase. Cartridges (Strata Gigatubes C_{18}-E; 5 g, 20 mL, Phenomenex, Germany) were activated with one volume of solvent B (90% (v/v) acetonitrile, 0.045% (v/v) trifluoroacetic acid) and equilibrated with two volumes of solvent A (100% (v/v) ddH_2O, 0.05% (v/v) trifluoroacetic acid), washed with 10% solvent B and eluted with 20 mL of 80% solvent B. The eluates were freeze dried and dissolved at 10 mg/mL in ddH_2O for cellular assays.

2.4. Collagen gel uterine contractility assays

Human uterine myometrial smooth muscle cells (hTERT-HM) (Condon et al., 2002) were cultured in Dulbecco's Modified Eagle Medium/F-12 containing 10% fetal bovine serum (Invitrogen, Carlsbad, CA, USA). Collagen gels were prepared from rat tail type 1 collagen (1.5 mg/mL) (Sigma, Ireland), and seeded in 24-well culture dishes with 150,000 cells per well. Cells in collagen gels were equilibrated overnight in serum free Dulbecco's Modified Eagle Medium/F-12. The aqueous extracts (100–400 μg/mL) and vehicle controls were added to the serum free media, and the gels released from the culture dish wells. Gels treated with 100 nM oxytocin were used as positive controls. The gel images were captured every 2–5 min in the first half hour and then at 20–30 min intervals thereafter until 4 h using a FluorchemTM 8900 imager and the area of the gels measured using AlphaEaseFC software (Alpha Innotech Corporation, San Leandro, CA, USA). Collagen contraction was determined in quadruplicate. A decrease in gel area correlates with an increase in contractility. The mean gel areas ± the standard error of the mean of each extract and the control un-stimulated cells in collagen at each time-point were determined, and the percentage increase in contractility for each extract calculated. One way ANOVA with Tukey's post-hoc analysis were used to statistically analyze the data (Prism, GraphPad Software Inc., La Jolla, CA, USA). Probability values of $P < 0.05$ were considered to be statistically significant (Fitzgibbon et al., 2009).

3. Results and discussion

We performed an ethnopharmacological study in Nigeria to document, analyze and validate the traditional use of frequently used herbal preparations during pregnancy, facilitate childbirth and to manage post-partum complications.

3.1. Ethnobotanical interviews and analysis

Seven main informants and 27 sub-informants participated in the survey and were not secretive about their knowledge on the medicinal properties of the plant species. The main informants, namely three traditional medical healers who also serve as birth attendants, one midwife, one local farmer, an artisan and a school teacher described altogether nine plant species and these were collected: *Calotropis procera* (Asclepiadaceae), *Commelina africana* (Commelinaceae), *Duranta repens* (Verbenaceae), *Hyptis suaveolens* (Lamiaceae), *Ocimum gratissimum* (Lamiaceae), *Saba comorensis* (Apocynaceae), *Sclerocarya birrea* (Anacardiaceae), *Sida corymbosa* (Malvaceae) and *Vernonia amygdalina* (Asteraceae). During the interviews, the main informants referred to sub-informants with traditional knowledge on the same

medicinal plants and their uses. The information obtained from the sub-informants was also included in the survey. The obtained plants are traditionally utilized during pregnancy, to treat conditions related to the birth-giving process and for postpartum care; their specific uses range from toning the uterus muscle, delayed labor, labor pains, dilation problems, contraction problems, for milk production or to aid postpartum uterine involution, prevent bleeding and postpartum hemorrhage. Medicinal plants are prepared in aqueous medium or are squeezed fresh before administration. Their local names, occurrence and protocol for preparation and application of the remedies are presented in Table 1. The route of administration employed for all the preparations is mainly oral. The information regarding the preparation and administration of the crude drugs are all obtained as handed over by spoken word. Most often leaves were utilized in herbal preparations while stem, barks, latex, root bark and fruits are used less frequently. Over half of the documented plants occurred commonly as weed while others can be found in the wild. All informants reported that the patients are free of complications during and after delivery when using the above described herbal remedies and they clarified the absence of commonly associated rituals such as repetitions, incantations, forbidden food and postures during the administration of the plant preparations. All plant species are used for the claimed medicinal property only. Interestingly, *Ocimum gratissimum* and *Vernonia amygdalina* are regularly consumed as food additives during pregnancy, normally in the form of soup that is called bitter leaf soup, to promote easy progression, strengthen or tone the uterus muscle and prevent complications, such as pain, bleeding and abortion. However, during labor, these two plants are administered fresh as squeezed leaves or aqueous extracts. Furthermore, one of the traditional healers advised that the plant *Sida corymbosa* should only be administered when the patient is already in the delivery room as it quickly induces labor and the birth process. The folkloric use of *Duranta repens* does not cut across various ethnic groups, but has only been reported by a particular group of traditional healers in the Federal Capital Territory.

To demonstrate the relative cultural importance of a certain medicinal plant species for its use during pregnancy, to facilitate childbirth and for postpartum care, we analyzed the survey data according to the use-mentions index (UM_I) as has been defined

Table 1
Ethnopharmacology of Nigerian plants used during pregnancy, childbirth and postpartum care.

Plant species (common name, local name(s))	Family	Location	Occurrence/ status	Preparation, administration and indication	Voucher no.	UM_I[h]			
						Total[i]	PR	BI	PP
Calotropis procera (Aiton) W.T.Aiton[a] (apple of sodom, Bomubomu-Nigeria)	Asclepiadaceae	Sokoto State	Occasional/ wild	stem bark powder is macerated in water for a few hours and extract is taken orally; used to dilate the birth canal during labor	ABU: 900219	0.235	*n.a.*[j]	0.235	*n.a.*
Commelina africana L.[b] (day flower, Gbagodo-Yoruba)	Commelinaceae	Abuja (FCT)[f]	Common/ weed	slimy aqueous extract from the leaves is taken orally when patient is stationary; taken during delayed labor	FHI: 108958	0.529	*n.a.*	0.529	*n.a.*
Duranta repens L.[c] (sky flower, yellow garden-Nigeria)	Verbenaceae	Abuja (FCT)	Common/ cultivated	leaves are boiled or decocted in water for a few days and is taken orally; to ease childbirth (pain)	FHI: 108959	0.353	*n.a.*	0.353	*n.a.*
Hyptis suaveolens (L.) Poit. (bush mint, Ebefue-Edo)	Lamiaceae[e]	Abuja (FCT), Edo State	Abundant/ wild	fresh leaves are extracted in aqueous medium after heating for oral administration; used to reduce the length of labor and labor pains; also used to repel malaria-causing insects	FHI: 108957	0.412	0.353	0.059	*n.a.*
Ocimum gratissimum L. (African basil, Efinrin-Yoruba)	Lamiaceae[e]	Abuja (FCT), Sokoto State, Edo State	Common/ cultivated	freshly collected leaves are squeezed in water together with a pinch of salt for oral administration; taken for painless delivery; steamed soup of leaves also used as food supplement; boiled leaves in aqueous medium used for gentle abdominal massage after delivery	FHI: 108961	0.500	0.294	0.176	0.029
Saba comorensis (Boj.) Pichon (rubber vine, Eciwo-Hausa or Orombo-Ososo)	Apocynaceae	Sokoto State[g]	Occasional/ wild	wine is used to extract the root bark; powdered root bark can also be boiled in water for several minutes, taken orally; used for many maternal conditions including labor induction; fruits are used as food supplement	ABU: 1173	0.088	0.029	0.059	*n.a.*
Sclerocarya birrea (A. Rich.) Hochst. (jelly plum, Loda- Hausa)	Anacardiaceae	Sokoto State	Occasional/ wild	stem bark is powdered and decocted in water for oral administration; for facilitating birth and milk production	ABU: 10701	0.118	*n.a.*	0.059	0.059
Sida corymbosa R.E.Fr.[d] (broom weed, Aramwemmvbi-Edo)	Malvaceae	Sokoto State, Edo State	Common/ weed	freshly collected leaves are pounded until slightly slimy; extract with water for oral administration; taken during labor to facilitate delivery	FHI: 108968	0.176	*n.a.*	0.176	*n.a.*
Vernonia amygdalina Delile (bitter leaf, Ebeoyara-Edo or Ewuro-Yoruba)	Asteraceae	Abuja (FCT), Sokoto State, Edo State	Common/ cultivated	food supplement in soup or fresh leaves are washed and squeezed in clean water; extract administered orally during labor; taken as soup regularly when delivery is close	FHI: 108960	0.853	0.676	0.176	*n.a.*

[a] Syn: *Asclepias procera* Aiton, *Asclepias gigantea Jacq.*, non L.
[b] Sample may contain traces of *Commelina benghalensis* due to habitat in the open field.
[c] Syn: *Duranta erecta* L.
[d] Sample may contain traces of *Sida acuta* due to habitat in the open field.
[e] Syn: Labiatae; [f]Federal Capital Territory.
[g] *Saba comorensis* was collected in Abuja (FCT).
[h] UM_I=use-mention index (as defined in Materials and methods).
[i] Use categories: total=all mentioned uses to facilitate and aid childbirth, PR=during pregnancy, BI=at birth, PP=postpartum care.
[j] Not available.

above. We have calculated a total score cutting across all three use categories and present the UM_I for each of the three main categories. The two plants with the highest total UM_I score are *Vernonia amygdalina* (0.85) and *Commelina africana* (0.53), respectively (Table 1).

3.2. Biological analysis and ethnopharmacological implications

All plants described from the informants were used to prepare aqueous extracts, which were then pharmacologically assayed for uterine contractility. Results of the *in vitro* contractility assays are summarized in Table 2. All of the extracts elicited significant increases in uterine smooth muscle cell contractility at the tested concentration range between 100 and 400 μg/mL; many of the extracts visibly contracted the gels immediately after release. The extracts of *Commelina africana*, *Sida corymbosa* and *Vernonia amygdalina* yielded the biggest increases in contractility in the uterine model, *i.e.*, 31.8% at 210 min, 32.8% at 210 min and 28.3% at 150 min, respectively. Most of the extracts maintained the contractile effect for 2.5–3.5 h, suggesting an added benefit in terms of being long-acting and having a sustained uterotonic action. Uterotonic agents in addition to inducing or augmenting labor are also used in the treatment of post-partum hemorrhage (Gruber and O'Brien, 2011). Globally, post-partum hemorrhage is the leading single direct cause of maternal mortality worldwide (Rajan and Wing, 2010). In Nigeria it accounts for nearly a quarter (23%) of maternal deaths and poor, rural women who have home births are more vulnerable to post-partum hemorrhage (Prata et al., 2012). The sustained, long-lasting effects of the characterized plant extracts could make them especially valuable to reduce the risks associated with postpartum hemorrhage (POPPHI, 2008). The pharmacological results are in good agreement with the relative cultural importance given by the UM_I, since the highest scored plants are generally those that yielded the biggest increase in uterine contractility, *i.e.*, *Commelina africana* and *Vernonia amygdalina*. Interestingly, *Sida corymbosa* whose extract resulted in a high increase in uterine contractility has a lower UM_I (0.18) since it has only been mentioned by three informants.

We have recently reviewed uterotonic plants, their bioactive ingredients and their mechanism-of-action on the uterus (Gruber and O'Brien, 2011). One or more of those uterotonic agents, including diterpenes, phenylpropanoid glucosides, heterocyclic aldehydes, fatty acids, saponins, sterols and polypeptides, may be responsible for the contractile properties of the nine plant species observed in this study. However, bioactivity-guided isolation and detailed phytochemical analysis will be subject to future studies. Previously, Jäger and co-workers reported uterine contraction of several Tanzanian plants that are traditionally-used for abortion (Nikolajsen et al., 2011). The list of these plants included *Commelina africana* and *Vernonia amygdalina*, which is in agreement with our results. *Vernonia amygdalina* may indeed contain a potent uterotonic agent, since aqueous extracts of this plant (100 mg/mL) induced uterine contraction amplitudes in guinea pig dams that were similar to those of ergometrine (Ijeh et al., 2011).

In summary, all nine plant species elicited a contractile effect on myometrial smooth muscle cells and this validates the rationale for their use by the traditional healers in Nigeria to aid or induce childbirth. Seven of these plants have been characterized using a cellular model for the first time. This information will help to improve the reproductive health of women with low access to primary healthcare in Nigeria and potentially in other parts of the world. Recent numbers claim that around 350,000 women die during pregnancy and childbirth annually (Hogan et al., 2010) and many of these women did not receive the necessary maternal care due to socio-economic factors (Prata et al., 2012), but they have access to

Table 2
Uterine contractility of Nigerian plant extracts.

Nigerian plant extracts (species name)	Concentration (μg/mL)	Contractility increase (%)[a]	Statistics (*P* value)	Time (min)
Calotropis procera	400	16.0	0.001	7
	200	17.8	*n.s.*[b]	210
		16.7	0.001	15
		17.0	0.001	140
Commelina africana	400	21.3	0.001	7
	200	31.8	0.001	210
		22.5	0.001	15
		31.2	0.001	150
Duranta repens	200	12.4	0.01	15
	100	21.0	0.001	15
		26.0	0.001	60
		12.1	*n.s.*	150
Hyptis suaveolens	400	12.1	0.01	7
	200	12.7	0.001	15
		11.9	0.001	140
Ocimum gratissimum	400	9.7	0.05	7
	200	17.3	0.001	20
		13.0	0.001	15
		12.0	0.001	140
Saba comorensis	100	16.9	0.001	15
		14.6	0.01	65
Sclerocarya birrea	200	16.4	0.001	15
		12.0	0.05	65
Sida corymbosa	400	15.7	0.001	7
	200	32.8	0.001	210
		23.6	0.001	15
		30.6	0.001	60
Vernonia amygdalina	200	16.7	0.001	15
	100	23.0	0.001	15
		28.3	0.001	150

[a] Only the largest percentage of increases in contractility of various concentrations of the plant extracts, at certain time-points are presented.
[b] Not significant.

Table A1
Ethnopharmacological questionnaire.

Questionnaire number				
Date			Voucher specimen number (to be added later)	
Informant or collector's information				
Name	Gender		Age	Profession
Taxonomic information				
Local name(s)	Scientific name(s)		Synonyms	Plant family
Taxonomic indicator (*e.g.*, exotic, indigenous, invasive)				
Plant Specimen information				
Short description of the plant				
Geography of location				
Village name	Topography		Habitat/vegetation	
Ethnological information				
Village culture			Language	
Family history			Interest level	
Medicinal/Pharmaceutical information				
Plant uses		Part used		When used
Preparation		Administration	Dosage	Application form/time
Effects/observation			Side effects	Contra indication
Special information on plant/notes				
Do you know other individuals (and how many) who have traditional knowledge about the use of this plant for the same/related purpose?				

Table B1
Summary and analysis of ethnopharmacological survey data.

Informants (first name, initial)[a]	Profession[b]	Location	Plant used	Specific use[c]	Level of use[d]
Ibrahim K	TMP/TBA	Wuse, Abuja	*Duranta repens*	$B_{3,4}$	b
			Commelina benghalensis	$B_{1,3,4}$	b, d
5 sub-informants	TMPs		*Duranta repens*	$B_{3,4}$	b
			Commelina benghalensis	$B_{1,3,4}$	b, d
Olaniyi BA	T	Wuse, Abuja	*Vernonia amygdalina*	$B_{3,4}$	a, d
			Hyptis suaveolens	$B_{1,3}$	a, d
10 sub-informants	F	Ososo, Edo	*Vernonia amygdalina*	$A_{0,2}$	a
			Hyptis suaveolens	A_7	a
Okuta K	F/TMP	Ososo, Edo	*Sida corymbosa*	$B_{1,3}$	a, d
Matthias S	TMP	Sokoto	*Sida corymbosa*	$B_{1,3}$	d
Musa K	T		*Sida corymbosa*	$B_{1,3}$	d
Patrick	AR	Kubwa, Abuja	*Ocimum gratissimum*	$A_{0,2}$, $B_{1,3}$	a, d
Chidi E	AR	Abuja	*Ocimum gratissimum*	A_0	a
Ajala	T/LMW		*Ocimum gratissimum*	A_0, $B_{1,3}$	a
Mbakwe	T		*Ocimum gratissimum*	A_0	a
Emma M	TMP/T	Sokoto	*Vernonia amygdalina*	$B_{3,4}$	a, b
			Sclerocarya birrea	B_4, C_5	b
			Ocimum gratissimum	A_0	a, c
			Calotropis procera	$B_{1,4}$	b
3 sub-informants	TMPs		*Sclerocarya birrea*	B_4, C_5	b, d
			Calotropis procera	$B_{1,4}$	b
Gallah A	TMP/TBA	Sokoto	*Saba comorensis*	B_1	b
2 sub-informants	TMPs		*Saba comorensis*	A_0, B_1	b, c
Fumilayo A	LMW	Ososo, Edo	*Vernonia amygdalina*	$A_{0,2}$, $B_{3,4}$	a, c
			Hyptis suaveolens	A_7	a
			Ocimum gratissimum	$A_{0,2}$, C_6	c
Ayi A	LMW		*Vernonia amygdalina*	A_0	a
			Hyptis suaveolens	A_7	a
			Ocimum gratissimum	A_0	c
Veronica	TMP		*Ocimum gratissimum*	A_0, $B_{1,3}$	a, b

[a] Main informants are marked in bold.
[b] Profession: AR=artisan, F=Farmer/local trader, LMW=local midwife, T=teacher, TBA=traditional birth attendant, TMP=traditional medical practitioner/healer.
[c] Specific use: A=during pregnancy, B=at birth, C=postpartum care; 0=taken as food supplement, 1=delayed labor/induce uterine contractions, 2=strengthen/tone uterine muscle, 3=reduce labor pains, 4=increase dilation, 5=induce/accelerate milk production, 6=aid uterine involution, prevent bleeding and postpartum hemorrhage, 7=repellent against Malaria carrying insects.
[d] Level of use: a=household level, b=TMP/prescription, c=community level, d=TBA/prescription.

medicinal plants, which potentially could save them (Nikolajsen et al., 2011). Documentation and biological validation of traditionally-used herbal remedies are ideal starting points for biological target-oriented drug discovery efforts and their pharmacological characterization may eventually lead to the development of novel uterotonic drugs.

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Appendix

Appendix.A

Ethopharmacological questionnaire. See Table A1.

Appendix.B

Summary and analysis of ethopharmacological survey data. See Table A2.

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