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Effect of *Khaya senegalensis* on uterine contractility in rats

Temidayo Olurishe*, Helen Kwanashie and Joseph Anuka

Department of Pharmacology and Clinical Pharmacy, Ahmadu Bello University, P.M.B. 1045, Zaria. Nigeria.

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Abstract

In a bid to establish a scientific rationale for the folkloric use of *Khaya senegalensis* the aim of this study was to determine the effect of the methanolic root bark extract of the plant on the rat uterus. With respect to uterine effects, the rat is the most appropriate animal model which can be extrapolated to man. Contractile response of isolated rat uterine preparations (approximately 2 cm strips) mounted in De-Jalon solution (in 25 ml organ bath) gassed with 95% oxygen / 5% carbon dioxide mixture at 32°C, were recorded using a microdynamometer. Both non-pregnant and pregnant isolated rat uterine tissues were challenged with oxytocin and acetylcholine as standard as well as with different concentrations of the extract followed by interaction studies. The results obtained from the experiments showed that the extract at concentrations between 0.3-3mg/ml (final organ bath concentrations) did not elicit any significant contractile properties but rather antagonized the contractile effects of oxytocin and acetylcholine. The antagonism was rapidly reversed in the non-pregnant uterine tissue while it was sustained in the pregnant uterine tissues. The present data therefore does not provide contractile basis for the purported use of *K. senegalensis* in abortions. Further studies are in progress to ascertain other possible mechanisms of abortions by the plant.

Keywords: *Khaya senegalensis*, Oxytocin; Rat uterus

Introduction

The WHO estimates that 80% of the people in developing countries rely on traditional medicine for their primary health care needs, and about 85% of traditional medicine involves the use of plant extracts (Farnsworth and Soejarto, 1985). This has continued to increase interest in the field of Traditional and Herbal Medicine with a view to establishing rationale for the use of plants used in alternative medicine. The plant *Khaya senegalensis* (A. Juss) family Meliaceae is a very widely distributed plant in the northern part of Nigeria as well as in several other African countries (Dalziel, 1955). The ethnomedical uses of the plant are as varied as the different cultures and geographical people that make use of the plant; for example, the stem bark of the plant has been used in the treatment of several conditions including stomach pain, malaria, fever and blennorrhagia (Mann *et al* 2003; Le Grand, 1989). Most of the preparations of *K. senegalensis* used are obtained from simple maceration procedures (Dalziel, 1955). In Guinea-Bissau, the hot water extract is used as a malaria remedy, while in Nigeria it has been reported to be used for treatment of ulcers and malaria fever (Olayinka *et al* 1992).In Guinea, the hot water extract of the

* Corresponding author. *E-mail address*: olurishe@hotmail.com Tel: +234 (0) 803 6005775, (0) 805 3668228
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bark is used as an abortificient and for menstrual troubles, administration being through the oral route. The hot water extract has also been reportedly used as an abortificient in Ivory Coast (Le Grand, 1989). Despite the folkloric use as an abortificient, literature search did not reveal any scientific basis for this use. As a first step to establishing a pharmacological basis for the use of *K. senegalensis* as an abortificient, the effect of the methanolic root bark extract on the rat uterus was studied.

Experimental

Drugs and chemicals. Acetylcholine (Sigma, US), Oxytocin (Novartis Switzerland), Methanol (British Drug House, UK), Stilbesterol (May and Baker).

Preparation of plant material. Plant identification was done at the taxonomic section of the Department of Biological Sciences, A.B.U. Zaria where a herbarium specimen was deposited with Specimen Voucher Number 900181. The root of the plant was obtained in January by manually digging into the ground. The root bark material was dried and size reduced to powder. The resulting powdered material was then packed and kept in a desiccator to prevent it from growth of fungi and other microorganisms. The extraction was carried out by 24-hour cold maceration using methanol, with 50 g of powdered material being macerated in 250 ml of methanol. Solvent recovery was carried out using a Soxhlet apparatus and the resultant extract was evaporated to dryness using an evaporating dish over a hot water bath at 65°C.

Animals. Non pregnant and pregnant female Wistar rats weighing between 220 and 275 g inbred in the animal house of the Department of Pharmacology and Clinical Pharmacy, Ahmadu Bello University, Zaria were used for this study. The non-pregnant rats were pretreated with 1 mg/kg stilbesterol intraperitoneally twenty-four hours before the experiment to bring them to oestrous stage. The animals were stunned with a blow on the head followed by decapitation. The abdomen was immediately dissected to expose the uterine horns, which were removed as soon as possible. Approximately 2 cm lengths of the uterine horns was each mounted isotonically in a 25 ml organ bath filled with De-Jalon solution of the following composition (in mM): NaCl 154, KCl 5.6, $NaHCO_3$ 1.7, $MgCl_2$ 1.4, glucose 5.5 and $CaCl_2$ 0.3. The solution was gassed with 95% oxygen-5% carbon dioxide mixture maintained at a constant temperature of 32°C. After a stabilization period of 30 minutes, the tissue was stimulated at least three times with oxytocin to establish constant responses. Pharmacological assessment of contractile activity was made using the isolated rat uterus preparations in a manner similar to that previously described (Veale *et al* 1989). The extract was then added in various concentrations to investigate if it possessed any intrinsic activity. This was then followed by interactions between the standard drugs (acetylcholine and oxytocin) and the extract. Tissue response/ contractility were recorded on Ugo Basil 7050 microdynamometer (Milan, Italy) through an isotonic transducer.

Results and Discussion

Both acetylcholine and oxytocin evoked contractions of the non-pregnant and pregnant uterine tissues in a concentration dependent manner (see Figures 1 and 2). This was as expected since oxytocin increases both the frequency and force of contraction in the mature uterus (Laurence *et al* 1999; Parker and Schimmer, 2001). The extract, unlike acetylcholine and oxytocin, did not produce any significant contractile effect on both the non-pregnant and pregnant uterine tissues, (see Figures 1 and 2). *K. senegalensis* however attenuated the effects of oxytocin

and acetylcholine in both non-pregnant and pregnant uteri – see Figures 3 and 4. This effect of the extract was not a sustained antagonism on the effect of oxytocin in the non-pregnant uterine tissue (Figure 3), as contractions obtained soon afterward were close to initial pre-inhibitory heights. This was also irrespective of pre-administration or co-administration of the extract with oxytocin. On the other hand, the antagonism of the effects of oxytocin in the pregnant uterus was more profound and sustained (Figure 4) to the extent that re-challenging the tissue after the antagonism by the extract failed to produce any contractile activity. The tissue however still contracted in response to stimulation with acetylcholine. This shows that the inhibitory effects of the extract were quickly reversed in the case of acetylcholine (but not for oxytocin). The abolition of the contractile response mediated by oxytocin by the extract (Figure 4), lends strong support to suggest that the extract does not possess uterine contractile properties within the concentrations used. The result of this interaction studies may suggest that the extract possesses some form of anti-oxytocic effects the exact mechanism of which remains to be elucidated. It has been suggested that attenuation of the effects of oxytocin is via the inhibition of prostaglandins (particularly prostaglandin PGI_2), which is known to inhibit endometrial contraction *in vitro* (Rall and Schleifer, 1985), or perhaps by the inhibition of ionic channels on the endometrial walls. If extrapolated to man, the sustained inhibition of the oxytocic effect in the pregnant uterus (Figure 4) may not augur well with pregnant women at term as their labour may be prolonged due to the antagonistic effects of the extract. However in earlier stages of pregnancy, this effect may be exploited in the prevention of threatened or habitual abortions occasioned by oxytocic action on the uterus. This would be similar to the use of ritodrine and fenoterol as uterine relaxants in Europe (Caritis, 1983). Terbutaline is also used as a tocolytic agent especially in delaying of premature labour (Johnson, 1993).

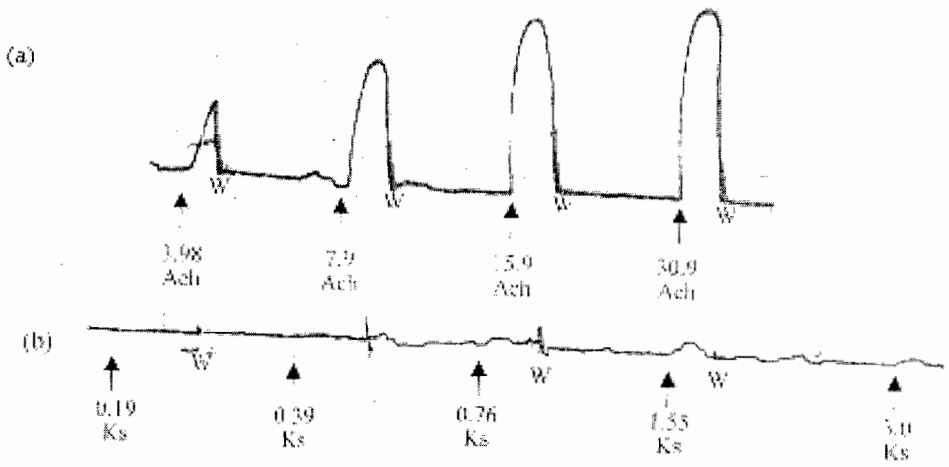

Figure 1: Effect of acetylcholine and *Khaya senegalensis* on the non pregnant rat uterus. (Sample of Several experiments)
Ach - acetylcholine in ng/ml; Ks - *Khaya senegalensis* in mg/ml and W - 2x Wash

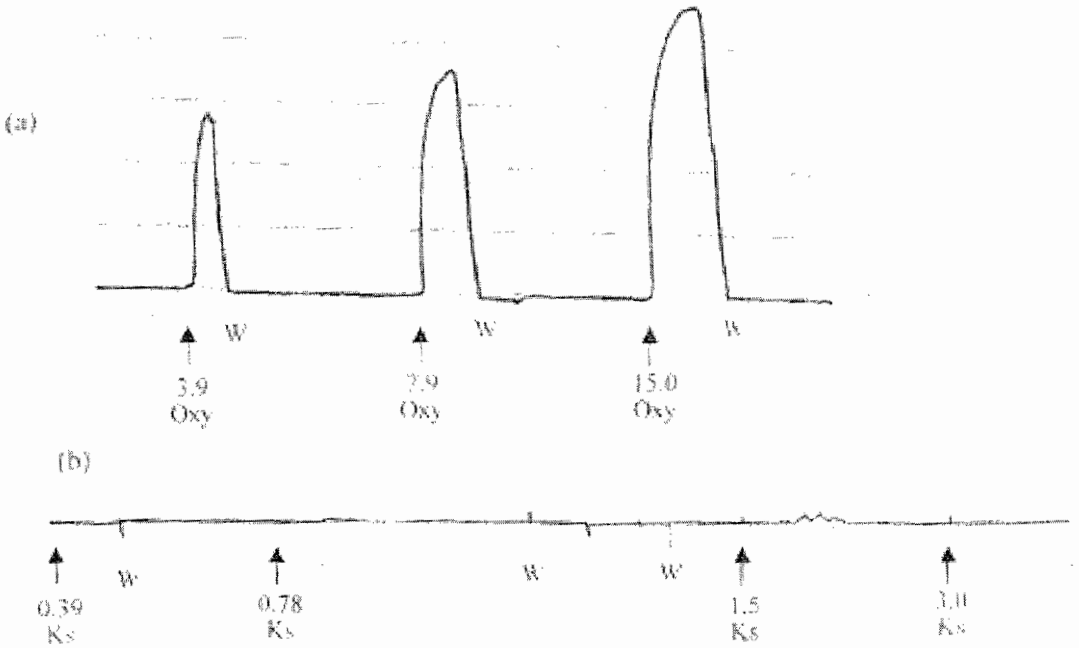

Figure 2: Effect of Oxytocin and *Khaya senegalensis* on the pregnant rat uterus. (Sample of Several experiments)
Oxy = Oxytocin in mg/ml; Ks = *Khaya senegalensis* in mg/ml and W = 3x Wash

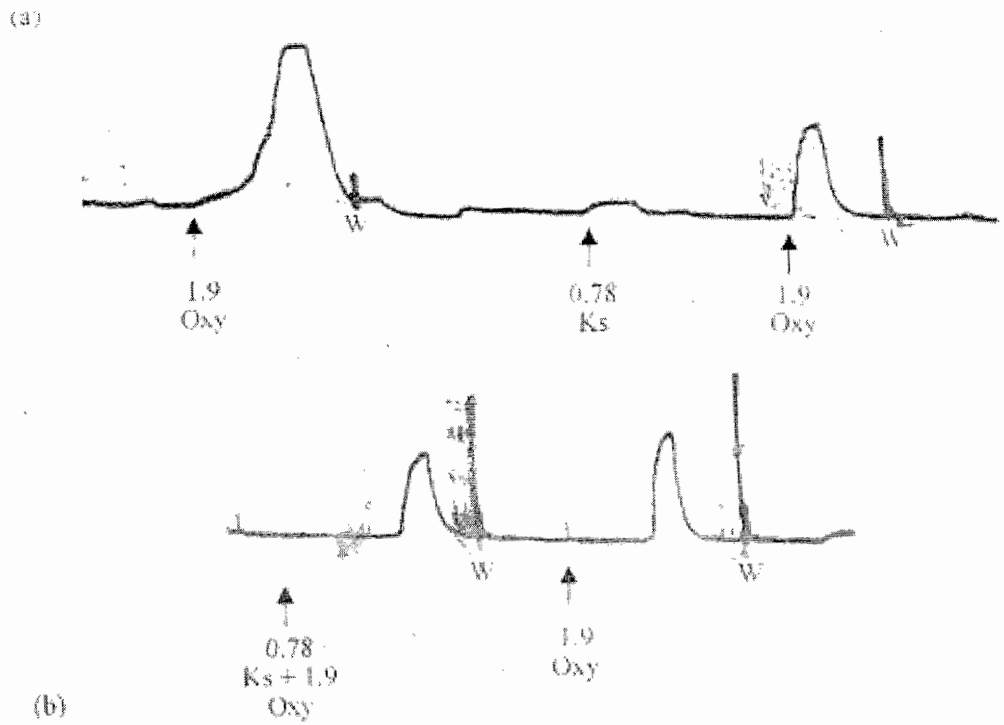

Figure 3: Effect of *K. senegalensis* on Oxytocin mediated contractions in the Non-pregnant rat uterus
(Sample of Several experiments)
Oxy-Oxytocin in ng/ml; Ks - *Khaya senegalensis* in mg/ml and W - 3x Wash
Upper panel - Ks administered before Oxy
Lower panel - Ks co-administered with Oxy.

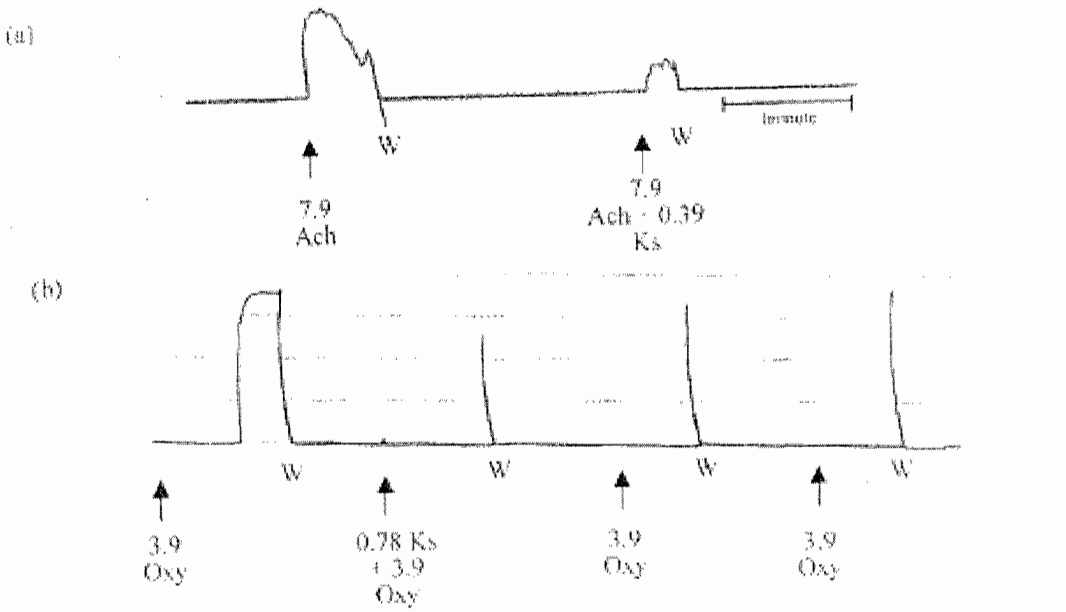

Figure 4: Effect of *K. senegalensis* on Acetylcholine and Oxytocin mediated contraction in the pregnant rat uterus
(Sample of Several experiments)
Ach - acetylcholine in ng/ml; Oxy - Oxytocin ng/ml; Ks - *Khaya senegalensis* in mg/ml and W - 3x Wash
Upper panel - Ks co-administered before Ach
Middle panel - Ks co-administered with Oxy
Lower panel - Continuation of middle panel.

It is therefore possible that the extract may act in a way similar to that of the tocolytic agents therefore proving to be a useful tool in the management of preterm labour. In conclusion this study has failed to justify the folkloric use of the plant *Khaya. senegalensis* as an abortificient agent. Rather, the results suggest that *K. senegalensis* may contribute to preventing abortion Further studies continue to explore other possible mechanisms or effects that may arise due to high concentrations of the extract while also conducting *in vivo* studies in pregnant animals.

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