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Carica papaya Leaves Might Cause Miscarriage

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Authors' contributions

This work was carried out in collaboration with all authors. Author AIA conceptualized and designed the study and also wrote the manuscript. Author EOO managed the analyses of the study. Author VNO managed the literature searches. Author UO wrote the protocol while Author JAE performed the statistical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Background: The use of *Carica papaya* leaves in folklore medicine for its antimalarial and antidiabetic activities is on the increase globally.
Aim: This was undergone to investigate if *C. papaya* leaves have the propensity to induce miscarriage during pregnancy.
Methods: Fresh and healthy leaves of *C. papaya* free from the disease were harvested from the culture garden of the Institute of Agricultural Research and Training, Moor Plantation, Ibadan. They were dried and extracted using Soxhlet apparatus and ethanol as the solvent. The toxicity test was carried out using the standard method. Thirty each of fertile male and female Wistar rats were taken for this study. After seven days of acclimatization, the female rats were separated into different cages and had estrus synchronization using Diethylstilbestrol dissolved in paraffin oil and administered at the dose of 1 mg/kg body weight. The male rats were then introduced into those each cages for mating process. After getting the confirmation of pregnancy test, the pregnant rats were grouped into the group of four. First group (Group A) was treated with normal saline, other groups (B, C, D) were treated with undiluted leaf extract of *C. papaya* for 24, 48 and 72 hours

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respectively. The animals were then observed daily if they littered. *In vitro* effects of the leaves on isolated rat uteri were determined following the standard method.
Results: Ethanolic leaf extract of *C. papaya* was safe in rats at the tested oral doses (500–2000 mg/kg). There was no mortality within the study period. In the *in vitro* experiment, *C. papaya* leaf extract elicited dose-dependent multiple contractions of the pregnant rat's uterus. 20% of animals treated with *C. papaya* leaf extract for 24 hours did no litter which suggestive that miscarriage has occurred. In the animals treated for 48 hours, only 60% littered which is also suggestive that miscarriage has occurred in the remaining 40% that did not litter. In the group treated with *C. papaya* leaf extract for 72 hours, 80% of the animals did not litter.
Conclusion: The results of this study suggest that papaya leaves contain active agents which could be toxic to the uterus. Thus, care should be taken in its use during pregnancy. However, this does not automatically translate to the same effect in humans; therefore, its effect on pregnant women can be further confirmed.

Keywords: Carica papaya; pregnancy; miscarriage; oxytocin; ethanolic leaf extract.

1. INTRODUCTION

Gestation is a vital part of the female reproductive cycle all over the world. It is also known as pregnancy. It normally consists of three trimesters and care should be taken during each trimester for safe delivery of the offspring into the world. After gestation/pregnancy period, oxytocin induces contraction for parturition (the process of giving birth) to occur [1]. Oxytocin has been reported to consist of nine amino acid peptide hormone secreted by the posterior pituitary that elicits milk ejection in female animals and women. In pharmacological doses, oxytocin can be used to induce uterine contraction and maintain lactation [2].

Oxytocin is a typical neural hormone just as vasopressin. The binding protein for oxytocin is known as neurophysin I while that of vasopressin is called neurophysin II. Both neurophysins are analogous in structure. The hormone-neurophysin complex stabilizes the hormone within the neurosecretory granules. Oxytocin is stored as neurosecretory granules and released from axonal terminals by calcium-dependent exocytosis [3,4]. Oxytocin is been best recognized for its important roles in the female reproductive system. It is released in increased volume during labour and after stimulation of the nipples. It is a facilitator for parturition and breastfeeding. However, recent researches have reported the role of oxytocin in various behaviours, including social recognition, orgasm, bonding, and maternal behaviours. oxytocin is believed to be involved in a wide variety of physiological and pathological functions such as ejaculation, sexual activity, pregnancy, milk ejection, penile erection, social bonding, uterine contraction, maternal behaviour, stress and probably many more [5]. Oxytocin is usually administered via the intravenous to induce contractions during childbirth. It is also available as a nasal spray to induce lactation post-partum. Oxytocin infusion near term will produce contractions that decrease the fetal blood supply. It is inactive orally because it is destroyed by gastric and intestinal enzymes [1].

Oxytocin has also been reported to be useful in stoppage bleeding postpartum. For this purpose, it can be administered intravenously or intramuscularly [6]. It is released into the bloodstream in response to stretching of the cervix and uterus during childbirth and with stimulation of the nipples during lactation [7]. In estrogen and progesterone primed rodents, injections of prolactin cause the formation of milk droplets and their secretion into the ducts but oxytocin leads to contraction of the myoepithelial cells lining the walls of the duct which results in the ejection of milk through the nipple [6]. Membrane receptors for oxytocin are available in uterine as well as mammary tissues. These receptors have been found to increase in number by estrogens and decrease by progesterone. The concomitant rise in estrogen and fall in progesterone occurring immediately before childbirth might probably explain the onset of lactation in some individuals before delivery [3,8]. The primer for the commencement of childbirth in humans is oxytocin secretion by specific cells of the fetus. The secreted oxytocin will activate certain cells of the placenta to produce and release prostaglandins. Oxytocin and prostaglandins synergize to stimulate the uterine myometria leading to a more vigorous and more frequent contraction [9]. At that point, the increasing emotional and physical stresses caused by these contractions activate the

mother's hypothalamus which signals for oxytocin released by the posterior pituitary. The elevated levels of oxytocin and prostaglandins trigger the rhythmic expulsive contraction of true labour [10].

Carica papaya belongs to the family of Caricaceae, and different species of Caricaceae have been used as a remedy against several diseases [11,12]. *C. papaya* was originally discovered in the southern part of Mexico, it is presently distributed over the whole tropical area. In particular, *C. papaya* fruit circulates widely, and it is accepted as food or as a quasi-drug. Many scientific investigations have been conducted to evaluate the biological activities of various parts of *C. papaya*, including fruits, shoots, leaves, rinds, seeds, roots or latex**.** The leaves of *C. papaya* have been shown to contain many active components such as papain, chymopapain, cystatin, à-tocopherol, ascorbic acid, flavonoids, cyanogenic glucosides and glucosinolates that can increase the total antioxidant power in the blood and reduce lipid peroxidation level [13].

Seed and fruit extracts of papaya have been reported to elicit bactericidal activities [14]. The leaves of papaya have been poultice into nervous pains, elephantoid growths and it has been smoked for asthma relief amongst tropical tribal communities. The antiplasmodial potency of ethanolic leaf extract of *C. papaya* against *Plasmodium berghei* in infected Swiss albino mice has also been reported [15]. *C. papaya* leaf extracts have also been used for a long time as an aboriginal remedy for various disorders, including cancer and infectious diseases.

C. papaya contains two vital biologically active compounds namely: chymopapain and papain which are widely used for digestive disorders [16]. It showed that papaya derived caricain, chymopapain, papain, and glycerin endopeptidase might boost acidic pH conditions and pepsin degradation. Another active component of *C. papaya* is lipase, which is a hydrolase, tightly bonded to the water-insoluble fraction of crude papain and is thus considered as a “naturally immobilized” biocatalyst [17]. According to folk medicine, *C. papaya* latex can cure dyspepsia and also applicable to external burns and scalds. Fruits, as well as seeds of papaya, are excellent antihelminthic and antiamoebic agents [18]. Dried and pulverized leaves are sold for making tea; also the leaf decoction is administered as a purgative for horses and used for the treatment of genetic-urinary system.

Fig. 1. *Carica papaya* Plant [15]

2. METHODOLOGY

2.1 Collection and Extraction of Plant Material

Fresh and healthy leaves of *C. papaya* free from the disease were harvested from the Institute of Agricultural Research and Training, Moor Plantation, Ibadan, Nigeria and were identified by a botanist. They were washed in running water to remove contaminants. They were air-dried at room temperature in open laboratory space for 14 days and milled into powder using an electronic blender (Moulinex). The extraction was done using Soxhlet apparatus and ethanol as the solvent according to the method described by Airaodion et al. [19,20]. About 25 g of the powder was packed into the thimble of the Soxhlet extractor. 250 mL of ethanol was added to a round bottom flask, which was attached to the Soxhlet extractor and condenser on a heating mantle solvent was heated using the heating mantle and began to evaporate moving through the apparatus to the condenser. The condensate dripped into the reservoir housing the thimble containing the sample. Once the level of the solvent reached the siphon, it poured back into the round bottom flask and the cycle began again. The process was allowed to run for a total of 18 hours. Once the process was completed, the ethanol was evaporated in a rotary evaporator at 35°C with a yield of 2.98 g which represents a percentage yield of 11.92%. The extract was preserved in the refrigerator for further analysis.

2.2 Oral Acute Toxicity Studies

Oral acute toxicity study was carried out according to the method described by Miller and Tainter [21]. Twenty-five rats were divided into five groups (1–5) consisting of 5 rats per group. Group A was given distilled water (10 ml/kg) while groups B, C, D and E were separately given 500, 1000, 1500, and 2000 mg/kg of the extract respectively. Treatments were administered orally by gastric intubation. The animals were observed for 24 hours post-treatment for signs of toxicity and then 48 hours for possible death.

2.3 Experimental Design and Animal Treatment

Thirty fertile male and thirty virgin female Wistar rats weighing between 170 and 200 g were purchased from the Central Animal House, College of Medicine, University of Ibadan, Nigeria. They were acclimatized for seven (7) days during which they were fed *ad libitum* with standard feed and drinking water and were housed in clean cages placed in well-ventilated housing conditions (under humid tropical conditions) throughout the experiment. All the animals received humane care according to the criteria outlined in the 'Guide for the Care and Use of Laboratory Animals' prepared by the National Academy of Science and published by the National Institute of Health. After the acclimatization period, the female rats were separated into its cages and had estrus synchronization using Diethylstilbestrol dissolved in paraffin oil and administered at the dose of 1 mg/kg body weight. A male was then introduced into each cage for mating. On the 7th day, the vaginal smear of each of the female rats was made on a clean glass slide by carefully inserting a cotton-tipped swab moistened with normal saline into the vaginal cavity of the rats and rolled gently against the wall before the withdrawal. The smear was stained with Giemsa and observed under the microscope to check for the presence of protein coagulates. After confirmation of pregnancy, the pregnant rats were grouped into four in the following order:

Group A: Normal saline *ad libitum* (control)
Group B: Undiluted *C. papaya* leaf extract *ad libitum* for 24 hours
Group C: Undiluted *C. papaya* leaf extract *ad libitum* for 48 hours
Group D: Undiluted *C. papaya* leaf extract *ad libitum* for 72 hours.

The animals were then observed daily till they littered.

2.4 *In vitro* Effect of *C. papaya* Leaf Extract on Isolated Rat Uteri

The method described by Airaodion et al. [22] was adopted: Matured pregnant female rats were sacrificed by stunning and decapitation. The lower abdomen was opened and the two uterine horns were harvested and transferred into De Jalon solution that continuously bubbled with air and maintained at 37°C (pH 7.4). The De Jalon solution was constituted such that each liter contained: NaCl (9 g), KCl (0.42 g), $CaCl_2$ (0.06 g), $NaHCO_3$ (0.5 g), and glucose (0.5 g). Each uterine horn was suspended vertically in a 35 mL organ bath using ligatures attached at one end to a tissue holder and at the other end to an isometric force-displacement transducer

connected to a digital physiological recorder (Medicaid Physiopac) for displaying isometric contractions. Resting tension in the muscle strip was readjusted, just sufficient to remove the slack. The preparation was allowed to equilibrate within 30 minutes of mounting. After recording regular rhythmic contractions, dose-response relationships were established for *C. papaya* leaf extract and other standard drugs used. For all administrations, a minimum time of 1 minute was allowed for individual tissue responses before being washed 3 times with De Jalon solution. The test substances were administered as final bath concentration (FBC).

Percentage (%) rise in Amplitude of Contraction was calculated as:

Percentage (%) rise in Amplitude of Contraction

$$= \frac{\text{Amplitude of Contraction with } C.papaya \text{ leaf extract} - \text{Basal}}{\text{Amplitude of Contraction with } C.papaya \text{ leaf extract (mm)}} \times 100$$

2.5 Statistical Analysis

Data were subjected to analysis of variance using Graph Pad Prism. Results were presented as Mean ± standard deviation. One way analysis of variance (ANOVA) was used for comparison of the means followed by Tukey's (HSD) multiple comparison test. Differences between means were considered to be significant at $p<0.05$.

3. RESULTS

3.1 Acute Toxicity Studies

Ethanolic leaf extract of *C. papaya* was safe in rats at the tested oral doses (500–2000 mg/kg). There was no mortality within the study period. However, there were behavioural changes such as depression, reduced motor activity and ataxia. There was also a slight increase in urine output.

All animals in the control group littered which is an indication that no abortion occurred as shown in Table 1. 20% of animals treated with *C. papaya* leaf extract for 24 hours did no litter which suggests that miscarriage has occurred. In the animals treated for 48 hours, only 60% littered which is also suggestive that miscarriage has occurred in the remaining 40% that did not litter. In the group treated with *C. papaya* leaf extract for 72 hours, 80% of the animals did not litter.

Table 1. *In vivo* activity of fresh *C. papaya* leaves extract on pregnant rats' uteri

Treatment groups	Number of rats per group	Pregnancy test	Type of treatment	Number that littered	Percentage (%) that littered
A	5	Positive	Normal Saline	5	100
B	5	Positive	Undiluted *C. papaya* leaf extract *ad libitum* for 24 hours	4	80
C	5	Positive	Undiluted *C. papaya* leaf extract *ad libitum* for 48 hours	3	60
D	5	Positive	Undiluted *C. papaya* leaf extract *ad libitum* for 72 hours	1	20

Table 2. *In vitro* effect of *C. papaya* leaf extract on isolated pregnant rats' uteri

Volume administered (mL)	Basal amplitude of contraction (mm)	The amplitude of contraction with *C. papaya* leaf extract (mm)	Percentage (%) rise in amplitude of contraction
0.05	5.00	21.17 ± 2.04	323.40
0.10	5.00	27.83 ± 2.83	456.60
0.20	5.00	29.14 ± 0.89	482.80
0.30	5.00	30.86 ± 1.27	517.20
0.40	5.00	31.11 ± 2.11	522.20

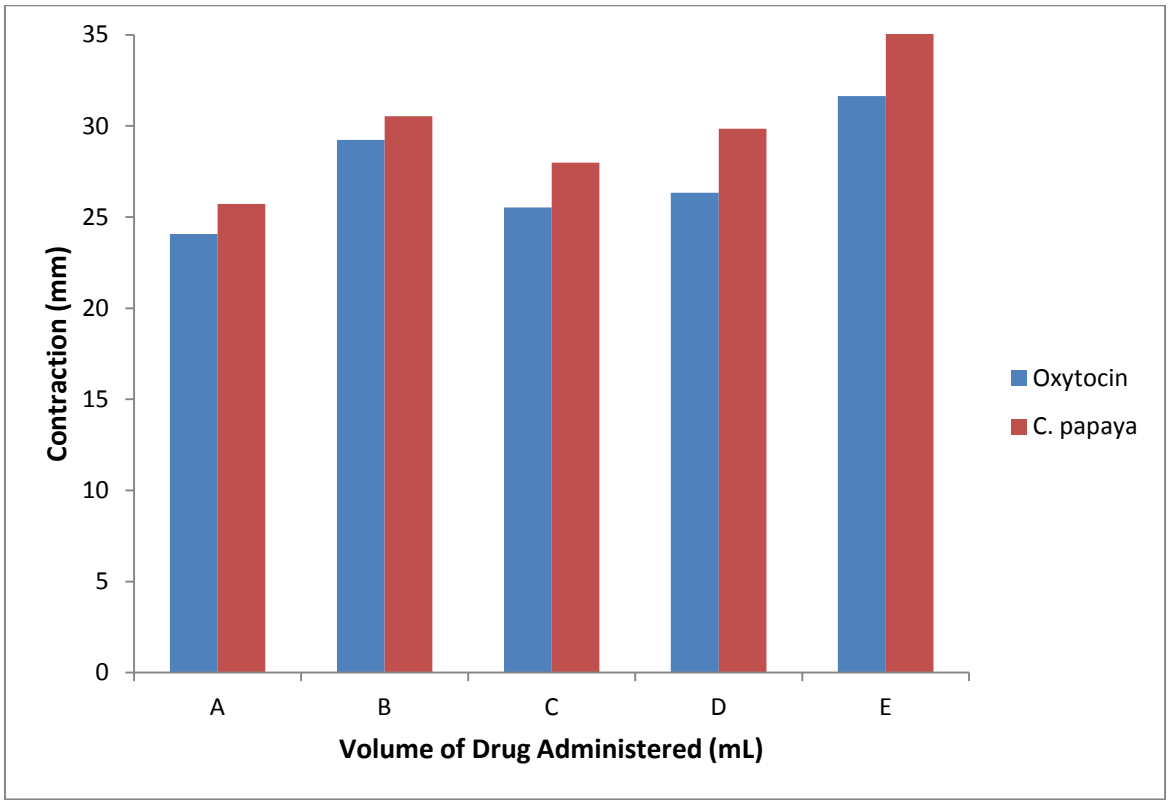

Fig. 2. Comparative effects of oxytocin and *C. papaya* leaf extract on an isolated pregnant rat uterus

The table showed that all doses of *C. papaya* leaf extract administered significantly induced contractions of the isolated rat uteri and this contraction increases as the dosage increases.

The effect of *C. papaya* leaf extract on an isolated pregnant rat uterus compared with that of standard uterotonic agent oxytocin showed that *C. papaya* leaf extract was giving slightly higher effect oxytocin at all doses.

4. DISCUSSION

Miscarriage is the natural death of an embryo or fetus before it can survive independently [23,24]. It is also known as spontaneous abortion and pregnancy loss [22]. Some use the cutoff of 20 weeks of gestation to describe miscarriage, after which fetal death is known as a stillbirth [25]. The most common symptom of a miscarriage is vaginal bleeding with or without pain. Miscarriage has been linked to several factors. The nutrition of a pregnant woman plays a major role in the status of the fetus. *C. papaya* leaves have been reported to possess antimalarial [15] as well as antidiabetic [26] properties. Consequently, it is used as a remedy to these ailments even in pregnancy. This study sought to investigate if it can induce miscarriage in an earlier pregnancy.

The result of the acute toxicity test of this study showed that *C. papaya* leaves are not toxic to health as no death was observed after 48 hours of administration of 500 to 2000 mg/kg body weight. The change in behaviour observed in the animals might be an indication that consumption of *C. papaya* leaves in high amount could lead to depression. Increase in urine output observed in the acute toxicity studies could also be suggestive that *C. papaya* leaves might inhibit antidiuretic hormone (vasopressin), a hormone involved in the regulation of micturition.

All the pregnant rats administered *C. papaya* leaf extract appeared physically healthy throughout this study. All animals in the control group littered which is an indication that no abortion occurred as shown in table 1. Only 80% of animals treated with *C. papaya* leaf extract for 24 hours littered which suggests that miscarriage has occurred in 20% of animals in that group. In the animals treated for 48 hours, only 60% littered which is also suggestive that miscarriage has occurred in

the remaining 40% that did not litter. In the group treated with *C. papaya* leaf extract for 72 hours, 80% of the animals did not litter. This might be an indication that *C. papaya* leaf extract induced miscarriage in 80% of the animals in that group. Animals that did not litter in their respective group were observed to be depressed which is one of the reported symptoms of miscarriage [27]. This result contradicts the findings of Airaodion et al. who treated animals with *Chrysophyllum albidum* [22] and *Ananas comosus* fruit juices [28,9] respectively.

All doses of *C. papaya* leaf extract administered significantly induced contractions of the isolated rat uteri ($p<0.05$) with 0.05, 0.1, 0.2. 0.3 and 0.4 raised the amplitudes of contractions from 5 mm to 21.17 $\pm$ 2.04, 27.83 $\pm$ 2.83, 29.14 $\pm$ 0.89, 30.86 $\pm$ 1.27, and 31.11 $\pm$ 2.11 respectively. The contractions induced by papaya leaves compared favourably with that of the standard drug oxytocin. This result corresponds with the findings of Airaodion et al. who treated animals with *Chrysophyllum albidum* fruit juice [22] and *Ananas comosus* fruit juice [28] respectively.

In the *in vitro* experiment, *C. papaya* leaf extract elicited dose-dependent multiple contractions of the pregnant rat's uterus. These effects were significantly different ($p<0.05$) from the basal contractions, with 0.40 mL of extract eliciting the highest increase in the amplitude of 522.20% (Table 2). This result also corresponds with the findings of Airaodion et al. who treated animals with *Chrysophyllum albidum* [22] and *Ananas comosus* fruit juices [28] respectively.

The effect of *C. papaya* leaf extract on an isolated pregnant rat uterus compared with that of standard uterotonic agent oxytocin showed that *C. papaya* leaf extract was giving slightly higher effect oxytocin at all doses (Fig. 2). This contradicts the study of Airaodion et al. [22] who reported greater effect for oxytocin at all doses when animals were treated with *Chrysophyllum albidum* fruit juice. It also contradicts another finding of Airaodion et al. [28] who reported greater effect for oxytocin at low doses but the lower effect at high doses when animals were treated with *Ananas comosus* fruit juice. Papaya leaf extract when administered to the isolated pregnant rat uteri induced multiple uterine contractions like that of oxytocin. This result suggests that *C. papaya* leaf extract may contain bioactive principles capable of inducing uterine contractions and as such could be used to facilitate labour or as an abortifacient. This might be due to the ability of the content of *C. papaya* leaves to bind to histaminergic (H_2) receptors present in the rat uterus [29], promoting calcium flux in the smooth muscles [9].

5. CONCLUSION

C. papaya leaf extract induced multiple contractions of the pregnant rat uteri following *in vitro* and *in vivo* administrations. This suggests that papaya leaves contain active agents which could be isolated and processed into pure uterotonic agents. Thus, it is recommended that care should be taken in the use of *C. papaya* leaves during pregnancy and its use in folklore medicine during pregnancy should be discouraged. However, the results observed in this study does not automatically translate to the same effect in humans, therefore, its effect on pregnant women can be further confirmed.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal ethic Committee approval has been collected and preserved by the author.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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