Research Article

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EFFECT OF UNRIPE *CARICA PAPAYA* ON UTERUS

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ABSTRACT
The present study was under taken to establish the uterine stimulant activity of aqueous extract of unripe *Carica papaya*. The effect of the aqueous extract of unripe *Carica papaya* was studied on isolated rat uterus and embryo. Uterine stimulant activity was compared with clinically available drug oxytocin and the effect on embryo was compared with misoprostol. In the *in vitro* model, *Carica papaya* showed contractile effect on the isolated uterus in diestrus stage and when administered orally in dose of 200 and 400 mg/kg to pregnant rats, resulted in gradual decrease in body weight indicating embryonic resorption. The present study confirms the uterine stimulant activity of aqueous extract of unripe *Carica papaya* fruit.
Keywords: *Carica papaya*; uterine stimulant; embryonic resorption.

INTRODUCTION

Uterine stimulants are medications given to cause a woman's uterus to contract, or to increase the frequency and intensity of the contractions. These drugs are used to induce or augment labor; facilitate uterine contractions following a miscarriage; induce abortion; or reduce hemorrhage following childbirth or abortion. The three uterotonics used most frequently are the oxytocin, prostaglandins, and ergot alkaloids[1]. The fruit of Papaya, (*Carica papaya*, Linn) is said to have compounds that act as the female hormone, estrogen and has been used in folk medicine to promote milk production, facilitate childbirth and increase the female libido. In some parts of the world, it is used to induce menstruation and is considered a uterine stimulant[2]. In India and parts of south-east Asia and Indonesia, consumption of papaya fruit is widely believed to be harmful during pregnancy, since papaya is believed to have abortifacient properties[3]. Women are strictly forbidden from eating ripe and unripe papaya for fear of its teratogenic and abortifacient effects during pregnancy. A study among 1200 women from all districts of Tamil Nadu in India showed that 82% of women avoided papaya during pregnancy. In Indonesia, Malaysia and Myanmar, different parts of the papaya have been used indigenously as abortifacients[4]. In this view, the present study was taken up to assess the effect of aqueous extract of unripe *Carica papaya* on uterus of pregnant and non-pregnant rat.

MATERIALS AND METHOD

Plant material

The unripe fruit *Carica papaya* was collected from the local market for the present study.

Preparation of plant extracts

Aqueous extract was prepared as per the method explained by Mahmood et al., (2007). The fruit was cleaned with water and the outer green thin layer was peeled and discarded. The underlying epicarp was peeled and 5 kg of it was blended with 1,250 ml of distilled water to a fine texture form using a blender. The mixture was filtered through fine muslin cloth and water was removed by rotor vaporizer. The filtrate was oven-dried at 40°C. The dried extract was used for the study[5].

Identification of phytochemical constituents

Aqueous extract of *unripe Carica papaya* was subjected to qualitative analysis for various phytoconstituents like alkaloids, glycosides, tannins, saponins, flavonoids and carbohydrates [6].

Animals

Laboratory bred Wistar rats, female weighing 150±5 gm and mice weighing 25-30 gm were obtained from the Central Animal Research Facility, NIMHANS, and Bangalore, India. The animals were kept in a well-ventilated animal house, under standard conditions (room temperature: 25 ± 3^{0}C, relative humidity: 28 to 31%) as per the guidelines of CPCSEA one week prior to use, under natural day and night cycle. The rats had free access to standard rat chow (Amrut Laboratory Animal feed, Karnataka India) containing protein 22%w/w, oil l4.13%w/w, fiber 3.15%w/w, ash 5.15%w/w, silica 1.12%w/w, and provided water *ad libitum*. The Institutional Animal Ethics Committee's approval was obtained before carrying out the experiment (Registration No. 152/99/CPCSEA).

Drugs and chemicals

Misoprostol tablets (Cytolog-200µg) were procured from Zydus Fortiza, East Sikkim. Oxytocin ampoules (pitocin-1ml) were procured from Gland Pharm limited Hyderabad. Sodium chloride, Potassium chloride, Calcium chloride, Sodium bicarbonate Glucose were obtained from SD fine chemicals, Pune, India.

Table 1: Effect of drugs on non pregnant rat uterus

Sl. No.	Oxytocin (I.U)	Contractile response (mm)	Unripe *carica papaya* (µg)
1	4	15	400
2	2	15	400
3	4	15	200
4	2	15	200
5	1	15	200
6	2	15	200
mean± SEM	2.5±0.50		266.7±42.15

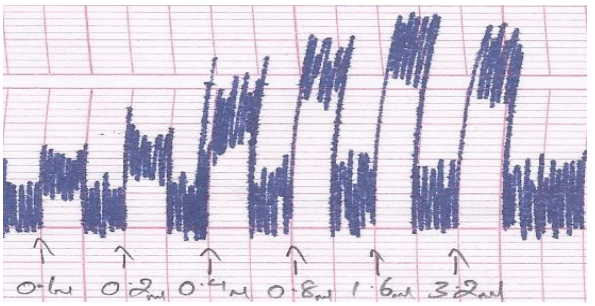

Figure 1: Effect of oxytocin on rat uterus

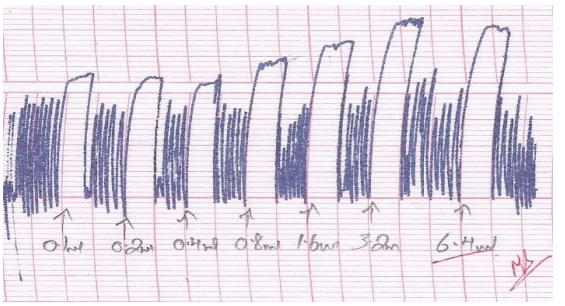

Figure 2: Effect of aqueous extract of unripe *Carica papaya* on rat uterus

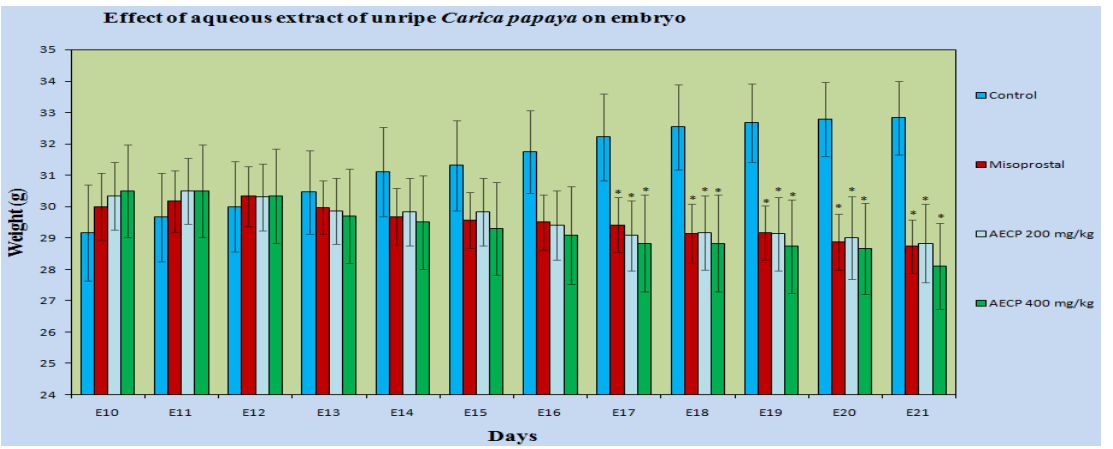

Figure 3: Effect of aqueous extract of unripe *Carica papaya* on embryo
(n=6) values expressed in mean ± SEM, one way ANOVA followed by Tukey's HSD post hoc test. * $P<0.05$v/s control. AECP-aqueous extract of *Carica papaya*

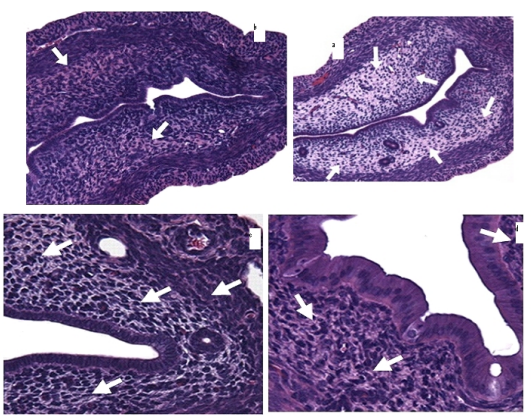

Figure 4: (a) TS of uterus of control mice showing hypertrophied superficial epithelial cells.
(b) T S of uterus of misoprostol (0.2µg/g) treated mice indicating no hypertrophy in the superficial epithelial cells.
(c) TS of AEUCP 200 mg/kg, treated mice uterus showing slight hypertrophy in the superficial epithelial cells.
(d) TS of AEUCP, 400 mg/kg treated mice uterus showing no hypertrophy in superficial epithelial cells

Effect of aqueous extract of unripe *Carica papaya* on isolated rat uterus

Eighteen Female rats, in dioestrous stage of oestrous cycle, weighing between 150 ± 5 gm were selected. Rat was sacrificed by decapitation and immediately, the entire uterus was removed from the body. One horn of the uterus was suspended in a muscle bath containing freshly prepared Locke Ringer's solution[7] and oxygenated with a mixture of 95% of oxygen and 5% of carbon dioxide. Bath temperature was maintained between 37-38 ºC. Contractions produced by the administration of 2 and 4 I. U of the standard preparation Oxytocin, were recorded using an isotonic transducer. When the contractions were complete, the solution in the bath was replaced by fresh solution and the muscle was relaxed for 4 min. Aqueous extract of unripe *Carica papaya* was added to obtain responses similar to those obtained with the standard preparation. The ratio between the two doses of the aqueous extract of *Carica papaya* was found to be the same as that between the two doses of the standard preparation and this ratio was kept constant throughout the assay. Six sets of experiment were repeated for aqueous extract of *Carica papaya and* standard preparation, Oxytocin[8].

Effect of aqueous extract of unripe *Carica papaya* on embryo

Swiss albino mice, weighing 25 to 30 g, were allowed for mating in 1 male: 3 females' ratio and pregnancy was confirmed by the presence of vaginal plug. Mice found to be positive for vaginal plug were separated from male counterparts, and divided into four groups of six animals (n=6) in each group. The animals of group1, administered with vehicle (deionized water), p.o. served as control. The animals of group 2 (standard) were administered misoprostol, 0.2 µg/g b.w. p.o. The animals of groups 3 and 4 were administered 200 and 400 mg/kg b.w. aqueous extract of *Carica papaya* respectively p.o twice daily. Respective groups of pregnant mice were given respective extracts orally (gastric intubations) from E_{10} until delivery, where, the first day of mating was considered as E_0 (embryonic day 0). Body weight of mice was recorded regularly. An increased body weight and distended abdomen by E_{10} of the mouse was considered as confirmation of pregnancy[9].

Histopathology study of pregnant mice uterus pretreated with aqueous extract of unripe *Carica papaya* and standard drug misoprostol

After the gestation period, animals were sacrificed by decapitation and immediately the uteri were dissected out for histopathology study[10].

Statistical analysis

The force of uterine contractions was represented as the maximum tension (g) above the base line during the period of contact with the test substances. The results for the isolated rat uterus method were expressed as the mean ± SEM[11]. The result for *in-vivo* method of the effect of aqueous extract of unripe *Carica papaya* on embryo was expressed by One-way ANOVA followed by Tukey's HSD test for post hoc analysis[9].

RESULTS

Qualitative analysis

The aqueous extract of unripe *Carica papaya* contains alkaloids, glycosides, tannins, saponins, flavonoids, and carbohydrates.

Effect of aqueous extract of unripe *Carica papaya* on isolated rat uterus

The tissue produced contractions for the standard drug, oxytocin at 2.5± 0.50 I. U whereas the test drug, aqueous extract of unripe *Carica papaya* at 266.7 ± 42.15 µg showed the same results.(Table 1, Figure 1 and Figure 2)

Effect of aqueous extract of unripe *Carica papaya* on embryo (in-vivo*)*

Mice administered with aqueous extract of unripe *Carica papaya* low dose 200 mg/kg experienced embryonic resorption. Mice given aqueous extract of unripe *Carica papaya* high dose 400 mg/kg also experienced embryonic resorption as the body weight continued to decreases until the day of delivery. None of the mice which was given deionized water experienced embryonic resorption, while all the mice given abortive drug misoprostol 0.2 µg/g b.w experienced embryonic resorption. (Figure 3)

Histopathology of mice uterus

The TS of uterus of control mice exhibited hypertrophied superficial epithelial cells (Figure 4). The TS of uterus of misoprostol (0.2µg/g) treated mice exhibited no hypertrophy in the superficial epithelial cells (Figure 5). Treatment with 200 mg/kg unripe *Carica papaya* fruit extract exhibited slight hypertrophy which may indicate termination of pregnancy during later term of pregnancy (Figure 6). Treatment with 400 mg/kg unripe *Carica papaya* fruit extract has not exhibited any hypertrophy which may indicate termination of pregnancy during early pregnancy (Figure 7).

DISCUSSION

In India and parts of south-east Asia and Indonesia, the fruit that is widely classified as harmful in pregnancy is papaya (*Carica papaya* L). Women are strictly forbidden from eating ripe and unripe papaya for fear of its teratogenic and abortifacient properties[3] during pregnancy. So, this study is an attempt to validate the folklore belief of abortifacient or uterine stimulant activity of unripe papaya fruit. It is known that the plasma level of progesterone is high in metesterus and diestrus stages while the level is low in estrogen dominated proestrus and estrus stages of the estrous cycle[12]. The observed contractile effect on the isolated uterine preparation in diestrus stage when administered with unripe *Carica papaya* fruit extract may be due to inhibition of progesterone levels in the plasma or may also be attributed to the elevation in estrogen levels in the plasma. The consistent and sustained contractile activity could be due to an uterotonic principle which might be a combination of enzymes (mixture of Proteolytic enzymes-papain and chymopapain), alkaloids and other substances[9]. From this study it is evident that the unripe *Carica papaya* fruit extract contains a uterotonic principle which can evoke sustained contractions of the uterus. It

seems likely that the oral intake of a large quantity of unripe papaya fruit may cause uncontrolled uterine contractions leading to abortion.

In the current study, 200 and 400 mg/kg unripe *Carica papaya* fruit extract treated animals showed gradual decrease in body weight indicating embryonic resorption. Green or unripe papaya fruit contains papain (proteolytic enzyme) in the latex and the latex content is very high in unripe papaya fruit. As reported in earlier studies, consumption of large quantities of unripe papaya fruit and subsequent ingestion of papaya latex can cause uncontrolled uterine contractions leading to abortion depending on the estrogen levels in the tissues that could be due to uterotonic effects of combination of enzymes[4]. Action of these proteolytic enzymes may be the reason behind the varied protein content and concentrations. However, further studies are required to identify the exact mechanism.

During pregnancy, certain physiological changes such as hypertrophy and hyperplasia take place. These occur under the influence of progesterone and estrogen during early weeks of pregnancy. These physiological changes revert to normal within few days after parturition. Treatment with 200 mg/kg unripe *Carica papaya* fruit extract exhibited slight hypertrophy which may indicate termination of pregnancy during later term of pregnancy. Treatment with 400 mg/kg unripe *Carica papaya* fruit extract has not exhibited any hypertrophy which may indicate termination of pregnancy during early pregnancy[13].

CONCLUSION

From the experimental study, it can be concluded that aqueous extract of unripe *Carica papaya* fruit possess significant uterine stimulant properties. The uterine stimulant activity may be due to the inhibition of progesterone levels in plasma or elevation of estrogen levels in plasma. From the findings of isolated rat uterus, mouse embryo and histopathological studies; it is concluded that the aqueous extract of unripe *Carica papaya* fruit at a dose level of 400 mg/kg b.w. possessed a significant uterine stimulant activity.

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