

# Effect of *Carica papaya* raw fruit extract using *in vitro* rat uterus preparations



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Submission: 06-03-2023

Revision: 28-06-2023

Publication: 01-08-2023

## ABSTRACT

**Background:** Uterine stimulants are medications used to induce/augment labor, induce abortion, and to prevent postpartum hemorrhage. Currently, available drugs carrying adverse effects, hence the present study is designed to study the effect of *Carica papaya* raw fruits extract in comparison with oxytocin using *in vitro* rat uterus preparations. **Aims and Objectives:** Primary and secondary aims of the present study were to evaluate the uterine stimulant effect and also the potency of *C. papaya* fruit extract using *in vitro* rat uterus preparations in comparison with oxytocin. **Materials and Methods:** A total of 6 female rats were taken and anesthetized with ether. By giving midline incision at abdomen from pubic symphysis, two horns of uterus were identified and collected from each rat. Uterus of each rat was subjected to Oxytocin 0.32 IU (standard), alcoholic extract of *C. papaya* 0.32 mg (AACP), and combination of various doses of AACP (0.64 mg, 1.28 mg, and 2.56 mg) and a fixed dose of Oxytocin (0.32 IU). Using Sherrington's kymograph, the uterine responses of each drug and combinations were studied in terms of height of the graph. **Results:** The mean contraction of uterus was 6.55mm and 2.26 cm, when Oxytocin (0.32 IU) and AACP (0.32 mg) injected, respectively. When combination of Oxytocin and different doses of AACP was injected, the uterus has shown dose-dependent response, i.e., 7.13 cm (Oxytocin 0.32 IU + AACP 3.2 mg), 8.08 cm (Oxytocin 0.32 IU + AACP 6.4 mg), and 9.01 cm (Oxytocin 0.32 IU + AACP 12.8 mg). **Conclusion:** AACP has shown dose-dependent uterine stimulant effect. Further studies are required to find out the possible mechanism behind the uterine stimulant activity of AACP.

**Key words:** *Carica papaya*; Oxytocin; Rat uterus

### Access this article online

#### Website:

<http://nepjol.info/index.php/AJMS>

DOI: 10.3126/ajms.v14i8.53027

E-ISSN: 2091-0576

P-ISSN: 2467-9100

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Medical Sciences



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## INTRODUCTION

Uterine stimulants are the drugs that cause contraction and increase the frequency or intensity of uterine contraction. These are the drugs used to induce labor, miscarriage, and reduce hemorrhage. There are three important uterotonic drugs, such as oxytocin, prostaglandin, and ergot alkaloids.<sup>1</sup> Oxytocin is a peptide hormone discovered in 1906 by Henry Dale. It plays a major role in human labor and birth.<sup>2</sup> It originates from paraventricular nuclei and supraoptic nuclei of the hypothalamus and gets transported to posterior pituitary.<sup>3</sup> Oxytocin shows uterine contractions by stimulating G-protein copulated mediated calcium release

in uterine myofibrils.<sup>4</sup> This process may further increase oxytocin concentration, leading to uterine contraction.<sup>5</sup> Oxytocin also causes contracted myoepithelium cells in female breasts for milk ejaculation. It is used not only in uterine contraction but also in postpartum hemorrhage.<sup>6</sup> There are some studies stating that the range of oxytocin is less in non-pregnant women, it may increase during pregnancy.<sup>7</sup>

Papaya is also called pawpaw, kates, and papaw. The botanical name is *Carica papaya*, belonging to the Caricaceae family.<sup>8</sup> It is a rich source of vitamins such as vitamin A, C, E, folate (B9), B6, Niacin (B3), riboflavin (B2),

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sodium, potassium, phosphorous, magnesium, and iron. The Unripened papaya consists of terpenoids, alkaloids, flavonoids, carbohydrates, glycosides, saponins, and steroids. All the parts of papaya have different uses. Papaya contains enzymes such as papain, chymopapain (CPN), lycopene, and fibrin. Papain and CPN help in the digestion of protein, so called proteolytic enzymes. It helps in reducing inflammation. CPN improves heart rate and blood pressure. Lycopene as a cancer fighting activity and fibrin helps in reducing the risk of blood clots and improving the quality of blood cells.<sup>9</sup>

The most used part of papaya is the fruit, bark, roots, and latex fruit parts having different uses. Leaves – treat dengue fever, reduce cancer growth, antimalarial and anti plasmodial activity, and improve digestion. Fruit, rich in pro-Vitamin A, Vitamin C, lycopene, dietary minerals, and fibers. Daniel one is the drug found in the fruit of papaya having antifungal activity against *colletotrichum gloeosporioides*. It is used as a laxative, prevents heart attack and stroke. Seeds have nephroprotective activity, antibacterial, anthelmintic, and antiamebic properties. Peel, used as a sunscreen, removes dandruff and muscle relaxant activity. Latex, a white milk substance found in unripened papaya used for uterine contraction, leading to miscarriage in pregnant women.<sup>9</sup> The fruits of *C. papaya* also act as a female hormone, estrogen, and are also used in folk medicine to promote milk production, facilitate child birth, increase female libido, and induce menstruation and uterine stimulation. Due to the abortifacient properties of papaya, in India, South, Asia, and Indonesia, consumption of ripened or unripened papaya fruit is harmful during pregnancy. There are 1200 women from different districts of Tamil Nadu and different areas of India avoid eating papaya during pregnancy.<sup>1</sup>

*C. papaya* contains crude papaya latex, proteinases, papain, and CPN, which are strong uterine contractants. Some studies rule out the possible mechanism of proteinases such as uterine contracting activity but also the action is not clearly noted.<sup>10</sup> The main aim of the study is to know the effect of Unripened *C. papaya* raw fruit extract, whether it causes uterine contraction compared with oxytocin.

### Aims

To Study the effect of carica papaya raw fruit extract on invitro rat uterus preparation.

### Objectives

1. To study the effect of carica papaya on invitro rat uterus
2. To study the effect of standard drug oxytocin on invitro rat uterus
3. To study the effect of combination of oxytocin and carica papaya on invitro rat uterus.

## MATERIALS AND METHODS

### Ethics and consent

The present experimental study was conducted in the central research laboratory, Department of Pharmacology, Mamata Medical College, Khammam. Prior clearance was obtained from the Institutional Animal ethical committee. Lr.No.IAEC/DP-09/C42 dated 1<sup>st</sup> April, 2013.

### Equipment used

The present study used Sherrington's kymograph.

### Drugs

Injection Oxytocin 1IU manufactured by sun pharmaceutical (Standard drug).

### Plants extract

This study used unripened *C. papaya* fruits (Test drugs).

### Biological solutions

De-Jalon's Solution was used as biological solution for the study.

### Experimental animals

A total number of 6 Swiss albino female rats weighing 175–225 gm were chosen for the study and they were kept fasting over night with water *ad libitum* 1 day before the experiment.

A total of 6 female rats were anesthetized with ether, by giving midline incision at abdomen from pubic symphysis, two horns of uterus were identified and collected from each rat and put them in a dish containing De-Jalon's solution which was constantly oxygenated. A thread is tied to each horn and then mounted in organ bath. The temperature was maintained at 35°C. Uterine tissue was kept in organ bath for 15 min complete relaxation before starting the experiment. The bath was aerated with oxygen.

### Procedure for the evaluation of uterine contraction activity

One of the uterine horns was suspended in the organ bath containing oxygenated De-Jalon's solution. Organ bath temperature was adjusted between 32°C and 35°C and speed of the drum fixed at slow (38 mts/revolution).

Using simple lever, different dilutions of oxytocin (0.1 IU, 0.2 IU, 0.4 IU, 0.8 IU, 1.6 IU, 3.2 IU, 0.64 IU, 1.28 IU, and 0.256 IU) contractile response were traced initially in terms of height of the graph in centimeters. Followed by the solution of organ bath was replaced by fresh De-Jalon's solution and waited for 4 min for complete relaxation of uterine tissue. After complete relaxation of uterine tissue, the extract of unripened *C. papaya* at various doses

**Table 1: Uterine contractile responses to oxytocin and papaya extracts in CM**

No of rat uterus used	Oxytocin 0.32 IU	AECP 3.2 mg	Oxytocin 0.32 IU + AECP 3.2 mg	Oxytocin 0.32 IU + AECP 6.4 mg	Oxytocin 0.32 IU + AECP 12.8 mg
Rat uterus number: 1	6.1	2.2	7	8.1	8.7
Rat uterus number: 2	6.5	2.2	7.5	8.2	8.8
Rat uterus number: 3	6.9	2	7.3	8.1	8.9
Rat uterus number: 4	5.8	2.5	7.1	8.5	9.2
Rat uterus number: 5	6.9	2.3	7	8.1	9
Rat uterus number: 6	7.1	2.4	6.9	7.5	9.5

AECP: Alcoholic extract of *carica papaya*

(0.2 mg, 0.4 mg, 0.8 mg, 1.6 mg, 3.2 mg, 6.4 mg, 1.28 mg, and 25.6 mg) were added one after another and responses were recorded. Followed by the solution of organ bath was replaced by fresh De-Jalon's solution and waited for 4 min for complete relaxation of uterine tissue. After complete relaxation of uterine tissue, combination of various doses of alcoholic extract of *C. papaya* (AECP) (0.64 mg, 1.28 mg, and 2.56 mg) and fixed dose of oxytocin (0.32 IU) was added and response was recorded.

### Statistical analysis

The tissue responses to oxytocin and unripe *C. papaya* extract were recorded (in terms of height of the graph) and analyzed using one-way ANOVA and Multiple Comparison with Dennett Test. Results were expressed as mean $\pm$ SEM and  $P < 0.05$  was considered statistically significant.

## RESULTS

In the present study, graded doses of oxytocin and papaya extract followed by the combination of graded doses of papaya extract plus fixed doses of oxytocin was studied for contractile response in rat uterine tissue (Table 1 and Figure 1).

When 0.32 IU of oxytocin was added to organ bath, the mean tissue contraction (Contraction in Cm) was  $6.55 \pm 0.209$  cm which is statistically significant ( $P < 0.05$ ). When 0.32 mg of papaya extract was added, the mean tissue response was  $2.26 \pm 0.07$  cm which is statistically insignificant ( $P > 0.05$ ) (Table 2).

The combination of graded doses of papaya extract (0.32 mg, 0.64 mg, and 1.28 mg) and fixed doses of oxytocin (0.32 IU) had shown dose-dependent uterine stimulant activity. When compared with standard drug, the tissue response was increased as a dose of papaya extract was increased, which is statistically significant ( $P < 0.05$ ) (Table 2 and Bar diagram 1).

## DISCUSSION

A standard drug Oxytocin I IU diluted to different concentration 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 0.64, 1.28, and

**Table 2: Mean response of uterine tissue to oxytocin, alcoholic extract of carica papaya and its combinations**

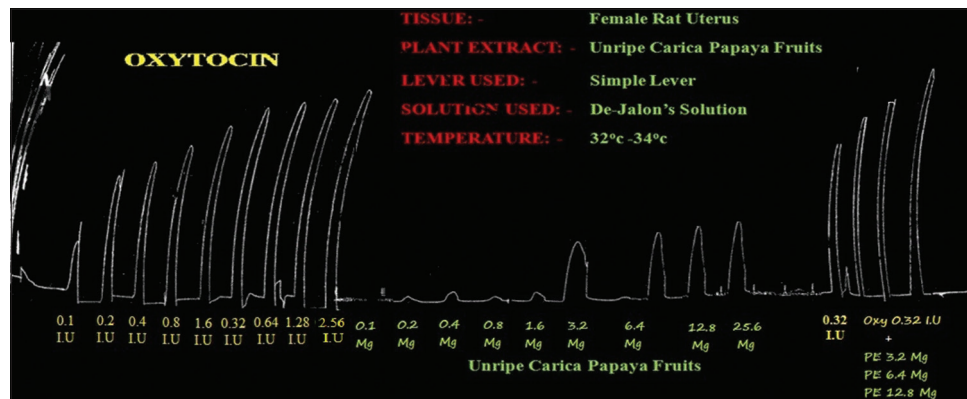
Doses	Height of contraction (graph) (cm), mean $\pm$ SEM
Oxytocin 0.32 IU	$6.55 \pm 0.209^*$
AECP 3.2 mg	$2.267 \pm 0.0714$
Oxytocin 0.32 IU+AECP 3.2 mg	$7.133 \pm 0.091^{**}$
Oxytocin 0.32 IU+AECP 6.4 mg	$8.083 \pm 0.132^{**}$
Oxytocin 0.32 IU+AECP 12.8 mg	$9.01 \pm 0.099^{**}$

\* $P < 0.05$  significant, \*\* $P < 0.001$  highly significant. AECP: Alcoholic extract of *carica papaya*, SEM: Standard error of mean

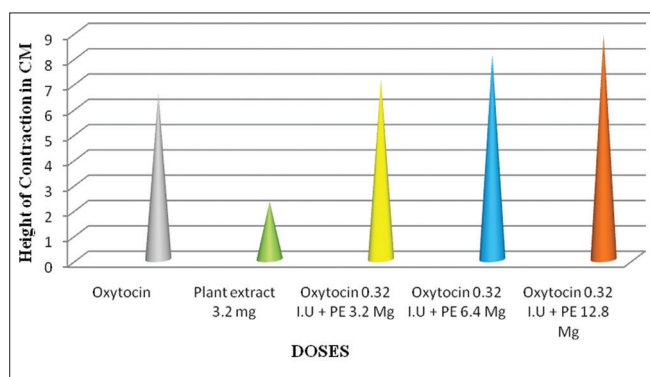
0.256 IU. The response was noticed when 0.1 IU of oxytocin was added to organ bath, as the concentration of standard drug increases there is an increase in response. The maximal response was observed at 0.32 IU. Various gradient doses of AECP were used (0.05, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, 12.8, and 25.6, mg), but initial response was observed at 0.32mg. Based on the maximal response of the standard drug (0.32 IU), three doses of AECP such as 3.2, 6.4, and 12.8 mg were selected and which were combined with oxytocin 0.32 IU and the response was compared with the response of oxytocin 0.32 IU (Table 1 and Figure 1).

In the present study, uterine stimulant effect was observed at the dose 3.2 mg of AECP, which was not statistically significant. However, in a similar study, *C. papaya* has found to be significantly uterine stimulant.<sup>1</sup> When the response of *C. papaya* was compared with oxytocin, the oxytocin response was statistically significant ( $P < 0.05$ ). Although AECP has produced similar response as *C. papaya*, which was not statistically significant, which is in line with in another study.<sup>10</sup> Combined effect of oxytocin and AECP was significantly higher than oxytocin effect alone, as the dose of AECP increases the response increases (Table 2).

The response to combination of various doses of AECP+Oxytocin 0.32 IU was (AECP 3.2 mg+oxyt 0.32 IU:  $7.133 \pm 0.091$  cm; AECP 6.4 mg+oxyt 0.32 IU:  $8.08 \pm 0.13$  cm; and AECP 12.8 mg+oxyt 0.32 IU:  $9.01 \pm 0.099$  cm) significantly higher than the response



**Figure 1:** Image showing tissue response to the standard, alcoholic extract of *Carica papaya* (AACP), and combination of standard and AACP extract



**Bar Diagram 1:** Response to the standard, alcoholic extract of *Carica papaya* (AACP), and combination of standard and AACP extract

produced by oxytocin alone ( $6.55 \pm 0.209$  cm) ( $P < 0.05$ ) (Table 2 and Bar diagram 1).

Previous study stated that A fully ripe papaya fruit may contain very little or a negligible quantity of the latex which may not provoke uterine contractions. Hence, the unripe or semi-ripe papaya contains abundant latex that produces marked uterine contractions may have an adverse effect during pregnancy and should be avoided.<sup>11</sup> Our study coincides with some study stated that intake of ripe, unripe, or semi-ripe papaya during pregnancy does not produces significant effect, unless the papaya contains latex, it produces uterine contractions and unsafe in pregnancy.<sup>11</sup> Another study also stated that pregnant women or women expected be pregnant should avoid intake of unripped or semi-ripped papaya because, papaya contains latex and papain, they can stimulate prostaglandins and oxytocin hormones. These hormones acts as a chemical signals to induce uterine contractions, miscarriage, and premature labour.<sup>12</sup>

### Limitations of the study

Our study is limited only at, comparing the submaximal doses of oxytocin with maximum doses of test drug but maximum dose of oxytocin with maximum dose of test drug is not compared

## CONCLUSION

Based on the findings of the present study, it is concluded that *C. papaya* raw fruit extract possess uterine stimulant activity but which is not significant. The combination of papaya extract and oxytocin had shown significantly higher effect than oxytocin alone. Further research is suggested to find out the possible mechanism behind the uterine stimulant effect of *C. papaya*.

## ACKNOWLEDGMENTS

The authors acknowledge the support given by staff members in the department.

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**Authors Contribution:**

**CHN**- Literature survey, Study design, preparation of figures, prepared first draft of manuscript; **NVN**- editing and manuscript revision, preparation of tables; **RK**- Coordination, editing and manuscript revision; **KVK**- Implementation of study protocol, data collection, data analysis, manuscript final preparation and submission of article.

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**Source of Funding:** Nil, **Conflicts of Interest:** None declared.