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Effect of the Aqueous Extract of *Carica papaya* (Caricaceae) Seeds on Endocrine Secretions in Male Wistar Rats

Yao Konan Bertin[1*], Kablan Kassi Jean-Jacques[2], Kouakou Koffi Roger[1]

[1]Faculty of Sciences and Technologies, Alassane Ouattara University, BPV 18 Bouaké 01, Côte d'Ivoire
[2]Department of Applied Biology and Health, Teaching Unit of Endocrinology and Reproductive Biology, Félix Houphouët -Boigny University, 22 PO Box 582 Abidjan 22, Côte d'Ivoire

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***Corresponding author:** Yao Konan Bertin
Faculty of Sciences and Technologies, Alassane Ouattara University, BPV 18 Bouaké 01, Côte d'Ivoire

Abstract | **Original Research Article**

As part of efforts to develop medicinal plants for the treatment of male infertility, a study was conducted on the effect of an aqueous extract of *Carica papaya* seeds on endocrine secretions in male Wistar rats. Toxicological analyses performed in accordance with OECD guidelines showed no signs of toxicity in the treated animals. Histopathological studies of the testes and epididymis revealed no structural abnormalities in these organs. Administration of the aqueous extract of *Carica papaya* seeds led to a significant increase in plasma levels of testosterone and luteinizing hormone (LH) in rats treated at a dose of 1000 mg/kg compared to controls. These results suggest that the aqueous extract of *Carica papaya* seeds boosted LH and testosterone and thus has a positive effect on male fertility at a dose of 1000 mg/kg body weight.

Keywords: Carica papaya, Testosterone, male fertility.

INTRODUCTION

Medicinal plants play a prominent role in healthcare systems around the world. According to the World Health Organization (WHO), approximately 80% of the population in developing countries relies on traditional medicine for their healthcare needs (WHO, 2013).

However, this medicine remains empirical, and the lack of precise dosages can lead to undesirable side effects (Diallo *et al.,* 1999; Traoré *et al.,* 2012). Consequently, the scientific validation of traditional uses through pharmacological, toxicological, and clinical studies is essential. Several researchers are calling for greater collaboration between traditional and modern medicine to foster an integrative approach to health (Jiofack *et al.,* 2010; Iwu, 2014).

Previous research has shown that administration of aqueous extracts of papaya seeds leads to suppression of spermatogenesis and impaired testicular cell morphology in male rats, suggesting a disruption of the hypothalamic-pituitary-gonadal axis (Aguwa *et al.,* 2005; Kaur *et al.,* 2021). Scientific studies evaluating their impact on the endocrine system, particularly male hormones such as testosterone and luteinizing hormone (LH), remain limited (Lohiya *et al.,* 2005). However, these hormones play a key role in regulating reproductive and metabolic functions in mammals (Smith and Walker, 2014). In light of the above, the overall objective of this study was to evaluate the effects of the aqueous extract of Carica papaya seeds on endocrine secretions in male rats.

MATERIALS AND METHODS

1- Materials

1-1-Animal materials

These studies were conducted on Wistar strain rats (Rattus norvegicus). Eighteen (18) rats, including twelve (12) males and six (6) females, were used. These animals were raised and fed at the animal facility of the École Normale Supérieure (ENS) in Abidjan.

1-2-6- Plant Material

The plant material used consists of seeds from *Carica papaya* (Caricaceae). These seeds were harvested in Cocody in February and May 2025.

2- Methods

2-1- Preparation of the aqueous extract of *Carica papaya*

Carica papaya seeds were dried and then ground into a powder using a blender. The resulting powder was

used to prepare the aqueous extract. Thus, 100 g of this powder was macerated in 2 liters of distilled water and stirred in a shaker for 24 hours. The resulting mixture was filtered successively through cotton wool and then through Whatman paper. The filtrate was evaporated in an oven at 40°C for 48 hours to obtain a dry aqueous extract, which was used to prepare the various doses of the aqueous extract of *Carica papaya* seeds for the different tests**.**

2-2- Phytochemical screening

The detection of these compounds is based on the principle that they induce chemical reactions in the presence of appropriate reagents (Wagner, Bladt, 2001).

2-3- Acute toxicity

This experimental study was conducted in accordance with OECD Guideline 423, adopted on December 17, 2001, for the testing of chemicals (OECD, 2001). Six (6) adult, nulliparous female rats weighing between 105 and 125 g were used. The rats were fasted for 14 hours prior to treatment while having free access to water. They were weighed and individually marked, then divided into two groups of three rats, one control group and one treated group, for identification purposes. After the fasting period, the control group received 1 ml/kg of body weight (bw) of distilled water. The treated group received 5000 mg/kg body weight of the aqueous extract of Carica papaya seeds via a suitable gastric tube. After administration of the various substances, the animals were observed hourly for 4 hours, then at regular intervals for 24 hours. Observation continued daily for 14 days to identify any signs of toxicity, namely tremors, mobility, diarrhea, eye color, coma, convulsions, lethargy, salivation, and death.

2-4- Subacute Toxicity

The subacute toxicity study was conducted in accordance with OECD Guideline 407. Twelve (12) male rats weighing between 105 and 125 g were divided into 3 groups of 4 rats each. The control group received 1 mL/kg body weight of distilled water, while groups 2 and 3 received 250 and 1000 mg/kg body weight, respectively, of the aqueous extract of Carica papaya seeds daily for 28 days. The animals were weighed daily to measure their body weights. At the end of the treatment, the animals were euthanized after ether anesthesia. Blood was collected from each animal into dry tubes for hormone assays, specifically testosterone and LH. Vital organs such as the kidney, liver, heart, lung, and adrenal gland (AG), as well as the genital organs—namely the testes, seminal vesicle, and epididymis—were removed, rinsed in 9% NaCl, and then preserved in 10% formalin for histopathological studies.

2-5- Histopathology of the Reproductive Organs

Histopathological sections of the harvested organs were prepared in several steps according to the method described by (Hould, 1984).

2-5-1- Fixation

The testis and epididymis were fixed in 10% formalin in a vial. These vials were carefully labeled to indicate the date of collection and the name of the organ.

2-5-2-Alcohol dehydration and clearing.

The organs are placed in labeled cassettes. The cassettes are then placed successively in baths of increasing alcohol concentrations (80°, 90°, and 96°) for one hour in the case of 80° alcohol and two hours in the case of 90° and 96° alcohol. They were clarified in three successive baths of toluene for one hour (first bath) and two hours (second and third baths) in order to remove traces of alcohol from the organs.

2-5-3-Impregnation

For two to three hours, the organs were impregnated in two baths of liquid paraffin. This procedure was performed in an oven at 50°C**.**

2-5-4-Paraffin embedding

At room temperature, the organs were embedded in paraffin using cassettes and molds. To facilitate demolding, the formed blocks were hardened in the freezer**.**

2-5-5-Microtome Sectioning

Histological sections 5 micrometers thick were prepared using a microtome. These sections yielded paraffin strips containing organs**.**

2-5-6-Deparaffinization of organs

The sections were spread onto microscope slides. These slides were then placed in an oven at 50 degrees Celsius for 30 minutes**.**

2-5-7-Staining of sections

The organs are deparaffinized again in three successive toluene baths, each lasting 15 minutes. They are then rehydrated for 5 minutes in three baths of alcohol of decreasing concentration (96%, 90%, and 80%). The sections are then rinsed with distilled water and stained in a hematoxylin-eosin bath. The sections are rinsed again with distilled water, and the organs are rehydrated in a series of alcohol baths of increasing concentration (80°, 90°, and 96°) for 5 minutes each to remove excess eosin. The organs were cleared one last time in a toluene bath for 15 minutes.

2-5-8-Mounting and Observation

The coverslips were mounted on the slides immediately after the organ sections were stained. A drop of Eukitt was placed on the organ section, which was immediately covered with a coverslip. Observation and measurements were performed using an OLYMPUS CX31 microscope connected to a computer equipped with VideoNet software. The magnifications (GX40 and GX100) allowed for the assessment of tissue abnormalities in the organs.

2-6- Statistical Analysis

The results were analyzed using XLSTAT software. The values were expressed as the mean followed by the standard deviation (M ± SD).

3- RESULTS

3-1-1- Phytochemical Composition

Phytochemical analysis of the aqueous extract of Carica papaya seeds revealed the presence of polyphenols, saponins, flavonoids, alkaloids, quinone compounds, tannins, sterols, and polyterpenes.

3-1-2 - Acute Toxicity

Treatment of rats with a single dose of 5000 mg/kg body weight resulted in no mortality after 14 days of treatment. Clinical signs of toxicity such as tremors, convulsions, salivation, diarrhea, lethargy, drowsiness, respiratory distress, oral bleeding, mobility issues, eye discoloration, coma, and death were not observed.

According to the OECD's Globally Harmonized System (GHS) 423, the LD50 is greater than 5,000 mg/kg body weigh.

3-1-3- Subacute toxicity of the extract

No clinical signs of toxicity, namely tremors, convulsions, salivation, diarrhea, lethargy, drowsiness, respiratory distress, oral bleeding, or coma, were observed during the 28-day period of daily treatment in rats treated with 250 and 1000 mg/kg body weight.

3-1-3-1- Body weight gain

Body weight gain in male rats treated with a dose of 1000 mg/kg body weight was 29 ± 1.00 g, compared with 34 ± 1.00 g observed in the control group. Statistical analysis showed no significant difference between the body weight gain observed in treated male rats and that in control male rats ($p > 0.05$), as illustrated in (**Table I**).

Table I: Effect of aqueous *Carica papaya* extract on body weight gain

Tested doses	Weight gain (g)
Control	34 ± 1a
250 mg/kg body weight	32 ,33 ± 1,52a
1000 mg/kg body weight	29 ± 1a

In each of these tables, the data are presented as mean ± standard deviation. Similarly, within the same column, values followed by the same letter a are not significantly different ($p > 0.05$).

3-1-3-2- Relative organ weights

At the end of the 28-day treatment at doses of 250 and 1000 mg/kg body weight, the mean values for the relative mass of the heart, liver, lung, kidney, and adrenal gland showed no significant variation compared to the controls ($p>0.05$); see (**Table II**).

Table II: Effect of aqueous *Carica papaya* extract on vital organs

Doses	Liver	Lungs	Kidneys	Heart	Adrenal Gland
Control	0,0415±0,0015a	0,00925±0,0023b	0 ,007± 0,001c	0,00375 ± 0,00d	0,00125±0,0005e
250 mg/kg body weight	0,0415±0,0064a	0,00875±0,0022b	0,0075±0,001c	0,004±0,0008d	0,001±0,00e
1000 mg/kg body weight	0,0345±0,0064a	0,00725±0,0009b	0 ,00675±0,0005c	0,00325±0,0005d	0,00125±0,0005e

In each of these tables, the data are presented as mean ± standard deviation. Similarly, within the same column, values followed by the same letter are not significantly different ($p > 0.05$)

3-1-3-3-Relative mass of the genital organs

The relative mass of the testis, seminal vesicle, and epididymis in rats treated with doses of 250 and 1000 mg/kg body weight daily for 28 days showed no significant variation compared to that of the control group ($p > 0.05$). The data are detailed in **(Table III)**.

Table III: Effect of the aqueous extract of *Carica papaya* on the reproductive organs

Doses	Testicle	Seminal vesicle	epididymis
Control	0,014±0,0017 a	0,047±0,0005 a	0,0022 ±0,0006 a
250 mg/kg body weight	0,015±0,0030 a	0,0415±0,0013 a	0,0024 ±0,0005 a
250 mg/kg body weight	0,014±0,0015 a	0,0415±0,0014 a	0,0023 ±0,0005 a

In each of these tables, the data are presented as mean ± standard deviation. Similarly, within the same column, values followed by the same letter are not significantly different ($p > 0.05$)

3-1-3-4-Effect of *Carica papaya* aqueous extract on hormone secretion

After 28 days of treatment with a dose of 1000 mg/kg body weight of Carica papaya aqueous extract, the results show an increase in LH concentration, which was 5.95 mg/ml in treated rats compared to 4.17 mg/ml in controls ($p>0.05$). The corresponding results are presented in **(Figure 1).**

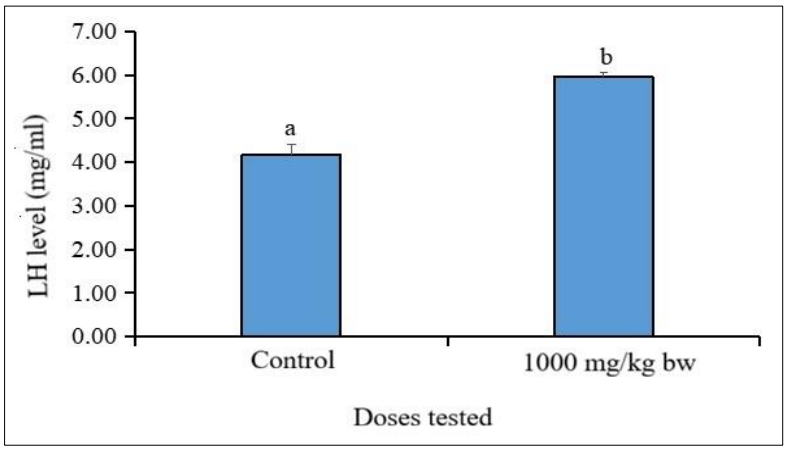


Figure 1: Effect of aqueous extract of *Carica papaya* seeds on LH secretion in male Wistar rats

he results also showed a significant increase in testosterone levels (4.35 mg/mL) in rats treated with 1000 mg/kg body weight of aqueous *Carica papaya* extract, compared to 2.7 mg/mL in control rats ($p > 0.05$). These data are presented in **Figure 2.**

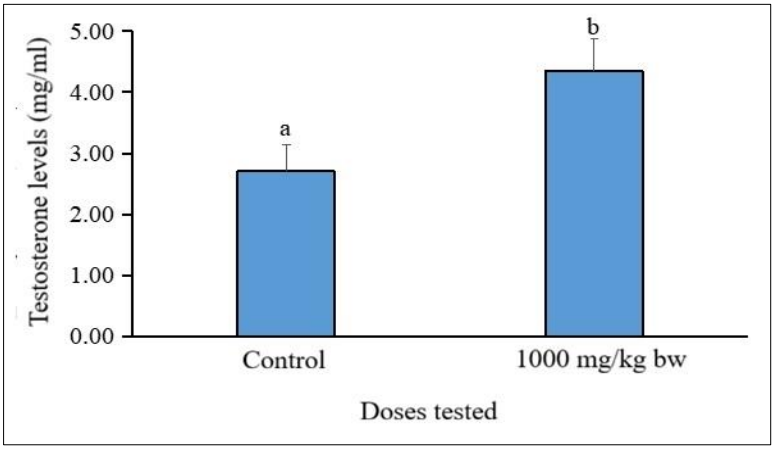
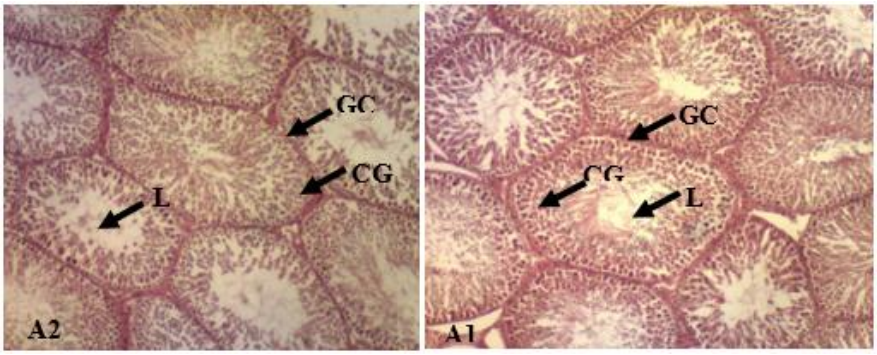


Figure 2: Effect of an aqueous extract of *Carica papaya* seeds on testosterone secretion in male Wistar rats

3-1-3-5. Histopathology of the Reproductive Organs

Histopathological examination of the testis and epididymis revealed no structural abnormalities (inflammation, hepatic cell necrosis, apoptosis) in rats treated with 1000 mg/kg body weight of aqueous extract of *Carica papaya* seeds, compared to those in control rats **(Figure 3).**



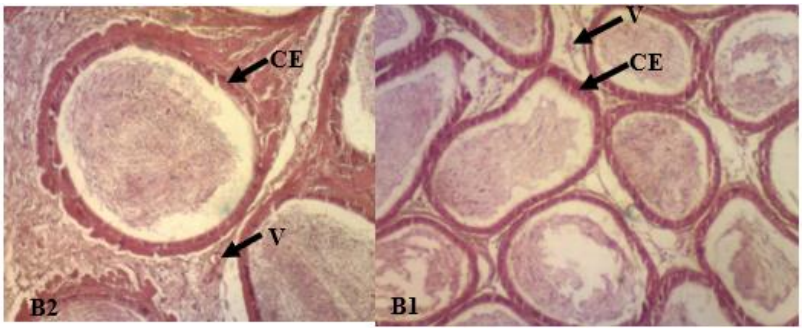


Figure 3: Histological sections of the testis (A) and epididymis (B) in control rats and rats treated with an aqueous extract of *Carica papaya* seeds

Staining: Hematoxylin-eosin; G x100
A1: Rat testis treated with 1000 mg/kg body weight of *Carica papaya* seed extract
A2: Rat testis treated with distilled water
B1: Rat epididymis treated with 1000 mg/kg b.w. of *Carica papaya* seed extract
B2: Rat epididymis treated with distilled water
GC: Connective tissue sheath; CG: Germ cells; L: Lumen; V: Vein; EC: Epithelial cells

3.2 DISCUSSION

Phytochemical analysis revealed the presence of polyphenols, flavonoids, saponins, alkaloids, quinone compounds, tannins, sterols, and polyterpenes in the aqueous extract of Carica papaya seeds. The coexistence of these metabolites suggests a wide range of biological properties, both beneficial and potentially toxic, corroborating the results reported by Maisarah *et al.,* (2014). Polyphenols and flavonoids are known for their strong antioxidant and anti-inflammatory potential. Their ability to scavenge free radicals and reduce oxidative stress helps protect cells from molecular damage, particularly at the level of DNA and lipid membranes (Onoja *et al.,* 2018). In a reproductive context, these compounds may protect germ cells and support hormonal regulation. Saponins, on the other hand, possess antimicrobial, immunomodulatory, and cholesterol-lowering properties (Francis *et al.,* 2002). However, several studies indicate that saponins may have a spermatotoxic and antifertile effect, as they alter membrane permeability and reduce sperm viability (Airaodion *et al.,* 2020). The alkaloids present in the seeds are known for their antiparasitic and analgesic properties, but also for their potential toxicity. Certain plant alkaloids have demonstrated male contraceptive activity by disrupting spermatogenesis and through hormonal modulation (Ezeonu *et al.,* 2017). Quinone compounds, often involved in the regulation of oxidative metabolism, are associated with antimicrobial and antitumor effects (Navarro-Tovar *et al.,* 2023). However, their cytotoxic activity could also explain certain adverse effects observed with prolonged use. The presence of tannins confers antimicrobial and antidiarrheal properties to the extract. However, due to their astringent nature and their ability to bind to proteins and minerals, tannins may have antinutritional effects, thereby reducing the bioavailability of certain essential nutrients, Administration of a single dose of 5000 mg/kg body weight resulted in no mortality or clinical signs of toxicity during the 14-day treatment period. According to OECD (2008) guidelines, an LD50 greater than 5000 mg/kg allows a substance to be classified as “practically non-toxic.” These findings are consistent with those of Kanadi *et al.,* (2019) and Akinmoladun *et al.,* (2020), who demonstrated that aqueous or methanolic extracts of Carica papaya exhibit low acute toxicity. This result suggests a wide margin of safety for experimental use. Indeed, repeated administration of the aqueous extract of Carica papaya seeds at doses of 250 and 1000 mg/kg for 28 days did not result in any clinical signs of toxicity. Several parameters were analyzed following this experiment. First, body weight gain showed no significant difference between the treated groups and the controls. This result indicates that the extract did not disrupt metabolism energy intake or the animals’ appetite (Oyelowo *et al.,* 2022). These findings are consistent with those of Saranraj and Sivasakthi (2018). Furthermore, the assessment of the relative weights of vital organs (heart, liver, kidneys, lungs, adrenal glands) and reproductive organs (testes, epididymis, seminal vesicles) revealed morphological stability, which is an important indicator of the absence of systemic toxicity (OECD, 2008). Ezike *et al.,* (2010) reached similar conclusions in their work. This morphological stability suggests an absence of cytotoxic or degenerative effects of the extract on these target organs. The absence of cytotoxic or degenerative effects could be explained by its composition of secondary metabolites (Elekofehinti *et al.,* 2017). These results indicate that the aqueous extract does not cause major anatomical changes, even though some studies report anti-fertility effects with organic extracts (Udoh and Kehinde, 2012). After 28 days of treatment, an increase in LH levels of 5.95 mg/ml was observed in rats treated with 1000 mg/kg compared to 4.17 mg/ml in the control group. Leydig cells are primarily responsible for the production of testosterone, a hormone essential for maintaining spermatogenesis. Testosterone acts in synergy with FSH to initiate or restart this process (Weinbauer and Nieschlag, 1993). An elevation in LH levels may indicate activation of the hypothalamic-pituitary-gonadal axis. The presence of flavonoids and saponins in the extract could explain this mechanism, as these compounds are known for their

modulatory role on pituitary secretion (Gauthaman and Adaikan, 2005). These results corroborate certain studies in which the administration of flavonoid-rich plants led to an increase in gonadotropins (Olagunju *et al.,* 2016). However, other authors have reported a decrease in LH with prolonged administration of Carica papaya extracts (Olorunnisola *et al.,* 2017), highlighting the influence of duration and type of extract. The aqueous extract also induced a 4.35 mg/mL increase in testosterone levels in rats treated with 1000 mg/kg compared to the control group, which had a level of 2.17 mg/mL. Testosterone is essential for spermatogenesis, the development of secondary sexual characteristics, and the maintenance of reproductive function. This increase can be attributed to the stimulation of Leydig cells by LH, but also to a direct action of polyphenols and saponins on steroidogenesis. Our results are consistent with those of Gauthaman and Adaikan (2005), who demonstrated that certain plant extracts that stimulate testosterone secretion act by modulating intracellular signaling pathways. The majority of secreted testosterone diffuses into the cytoplasm of Sertoli cells, where it binds to ABP (Androgen Binding Protein). This binding promotes the maturation of the seminiferous epithelium as well as the optimal functioning of the genital tract and the composition of seminal fluid. When excess testosterone is produced, the unbound fraction enters the bloodstream and plays a dual role: on the one hand, it positively stimulates the genital tract and accessory glands, and on the other hand, it induces negative feedback on LH secretion, either indirectly via hypothalamic neurons or directly at the level of the gonadotropic cells of the pituitary gland. This regulatory mechanism can disrupt spermatogonial differentiation and compromise the maintenance of spermatogenesis. In contrast, Olorunnisola *et al.,* (2017) observed a decrease in testosterone levels following prolonged treatment, suggesting a dose- and time-dependent effect. Udoh *et al.,* (2005) also observed a significant decrease in serum testosterone levels, accompanied by impaired spermatogenesis and reduced testicular weight after administering 50 mg/kg/day of aqueous Carica papaya seed extract for 8 weeks to male albino rats. Eno *et al.,* (2011) also reported that administration of aqueous Carica papaya seed extract at 100 mg/kg body weight for 28 days to male Wistar rats resulted in a decrease in LH and testosterone levels, as well as an increase in the number of abnormal spermatozoa. These results reinforce the notion that certain bioactive compounds, particularly saponins and alkaloids, act as negative endocrine modulators. These observations support the use of Carica papaya seeds as a natural contraceptive agent (Memudu *et al.,* 2021). These authors also demonstrated inhibition of Leydig cells, which are responsible for testosterone synthesis, likely due to disruption of the hypothalamic-pituitary-testicular axis. These findings indicate that the impact of Carica papaya on endocrine function remains complex and requires further investigation. Histological examination of the testes and epididymis revealed no abnormalities, such as inflammation, apoptosis, or cellular necrosis, in rats treated with the aqueous extract. This indicates that, despite the observed hormonal changes, tissue integrity is preserved. These results are consistent with those of Uche-Nwachi *et al.,* (2001), who showed that the antifertility effect of Carica papaya seeds is often manifested by functional alterations in spermatogenesis rather than by morphological lesions.

CONCLUSION

The study on the effect of aqueous extract of *Carica papaya* seeds on endocrine secretions in male Wistar rats provided a better understanding of the physiological potential of this tropical plant in the field of hormonal regulation. The results showed that administration of aqueous extract of *Carica papaya* seeds, although it did not cause any acute toxicity or significant changes in body weight or the weight of vital and reproductive organs, led to a significant increase in plasma levels of testosterone and luteinizing hormone (LH) in rats treated with a dose of 1000 mg/kg compared to the controls. These results suggest that the aqueous extract of *Carica papaya* seeds boosted LH and testosterone and thus has a positive effect on male fertility at a dose of 1000 mg/kg body weight.

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