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Antispermatogenic Effect of Seeds Extract of Papaya (*Carica papaya* L.) in Mice

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Abstract To enrich new evidence about the anti-fertility activity of seeds extract of papaya (*Carica papaya* L.) in test animals, especially mice. Male mice (n=20) were grouped into four. The first group received only distilled water containing 1% CMC as the control. Group 2, 3 and 4 consecutively received papaya seeds extract of 2, 4 and 8 mg/40 g body weight. All treatment administered orally using stomach sonde once daily for 35 days. Study parameters assessed were the number spermatogonia, spermatocyte and spermatid cell counts, diameter and epithelial thickness of seminiferous tubules of the testis. There is no significant different in the number of spermatogonia between treatment groups. Spermatocyte and spermatid cells significantly decreased by the extract, especially at the highest dose. Additionally, the diameter and epithelial thickness of seminiferous tubules of testis are siginicantly reduced by the extract at the dose of 8 mg/40g body weight. Papaya seeds extract as potential to be used as anti fertility agent.

Keywords: Carica papaya, contraceptives, papaya seeds, antispematogenic, antifertility

1. Introduction

There are many medicinal plants that are reported to have potential as anti-fertility agents. However, to be acceptable the ingredient must be eligible, among others causing azoospermia (cement), easy to use, no side effects and toxic, not interfere with libido or sexual behavior and is reversible [1].

Papaya (*Carica papaya* L.) is one of tropical plants worth considering to be developed as a contraceptive. In Langur monkey seeds extract of papaya revealed to cause tubules of testis shrunken, vacuolation of Sertoli cells and abnormalities of germ cells, and inhibition of steroidogenic function of Leydig cells [2]. In Wistar rats, seeds extract of this plant at the dose of 50-200 mg/kg caused hypertrophy of pituitary gonadotrophs, gradual degeneration of germ cells, Sertoli cells and Leidig cells as well as germinal epithelium, progressive collapse dan shrinked villi of seminal vesicles [3]. In mice, treatment of seed extract of papaya for 7 days caused the decrease in sperm concentration, motility and viability [4].

Although the results of research on the antifertility activity of papaya seed extract showed a positive trend, but in-depth verification of the effects of these plant preparations on test animals is still required as recommended by the World Health Organization [5]. This study is intended to enrich new evidence about the anti-fertility activity of papaya seed extracts in test animals, especially mice. In the study reported Wiryawan, giving extract only for 7 days. In this research, papaya seed extract was given for 35 days, based on the duration of one cycle of spermatogenesis.

2. Materials and Methods

Plant Materials

Seed samples of papaya (*Carica papaya*) used in the study were originated from ripen fruit collected from a local papaya farmer in suburb of Bandar Lampung, Indonesia. The sun dried seeds were milled into powder and then macerated using methanol. After vacuum evaporation, the viscous extract then suspended in 1% CMC in distilled water in accordance with the prescribed treatment doses.

Animals and Treatment

Twenty male Swiss albino mice, aged 4 months and weighing 25-30 g from Lampung Veterinary Center, Indonesia, were used and divided into four groups. The first group received only distilled water containing 1% CMC as the control. Group 2, 3 and 4 consecutively received papaya seeds extract of 2, 4 and 8 mg/40 g body weight. All treatment administered orally using stomach sonde once daily for 35 days. On day 36 all mice were sacrificed and the testes were taken for histological preparation using formalin as a fixative and stained using hematoxylin-eosin. Microscopic slides of the testes were then observed using light microscope at 400x magnification.

Study Parameters and Data Analyses

Study parameters assessed were spermatogonia cell counts, spermatocyte and spermatid cell counts, diameter and epithelial thickness of seminiferous tubules of the testis. To detect intergroup differences one-way ANOVA was performed, followed by Fisher's least significant difference (LSD) test to detect differences between individual groups at the $p < 0.05$.

3. Results

Spermatogenic cell count of mice after daily treatment of papaya seeds extract for 35 days are shown in Table 1. There is no significant different in the number of spermatogonia between treatment groups. However, both spermatocyte and spermatid cells significantly affected by the extract, especially at the highest dose. Table 2 depict the effect of papaya seeds extract on the diameter and epithelial thickness of seminiferous tubules of testis. The data showed that at the dose of 8 mg/40g body weight papaya seeds extract significantly decreased diameter of seminiferous tubules. Furthermore, in comparison to control, all treatment doses significantly decreased the epithelial thickness of the tubules. The histological changes in diameter and epithelial thickness of the seminiferous tubules of mice of different treatment are visualized in Fig.1.

Table 1: Spermatogenic cell counts of mice after papaya seeds extract treatment for 35 days

Papaya seeds extract	Spermatogonia	Spermatocytes	Spermatids
0 (mg/40g bw)	59.60 ± 3.78^{a}	185.40 ± 23.00^{a}	176.60 ± 28.43^{a}
2 (mg/40g bw)	53.80 ± 4.32^{a}	138.80 ± 30.06^{b}	152.40 ± 18.03^{a}
4 (mg/40g bw)	51.00 ± 13.09^{a}	108.60 ± 24.79^{bc}	137.20 ± 14.42^{ab}
8 (mg/40g bw)	49.80 ± 7.66^{a}	90.04 ± 14.63^{c}	127.20 ± 21.34^{b}

Data are presented as mean±SD. Values in the same column followed by the same superscript are not significantly different at $\alpha<0.05$ by LSD test

Table 2: Diameter and epithelial thickness of seminiferous tubules of mice after papaya seeds extract treatment for 35 days

Papaya seeds extract	Diameter of Seminiferous Tubule (µm)	Thickness of Seminiferous epithelium (µm)
0 (mg/40g bw)	192.60 ± 8.26^{a}	45.30 ± 5.46^{a}
2 (mg/40g bw)	179.80 ± 7.59^{a}	26.50 ± 7.00^{b}
4 (mg/40g bw)	177.80 ± 9.8^{ab}	24.60 ± 4.70^{b}
8 (mg/40g bw)	176.20 ± 18.68^{b}	21.10 ± 2.43^{b}

Data are presented as mean±SD. Values in the same column followed by the same superscript are not significantly different at $\alpha<0.05$ by LSD test

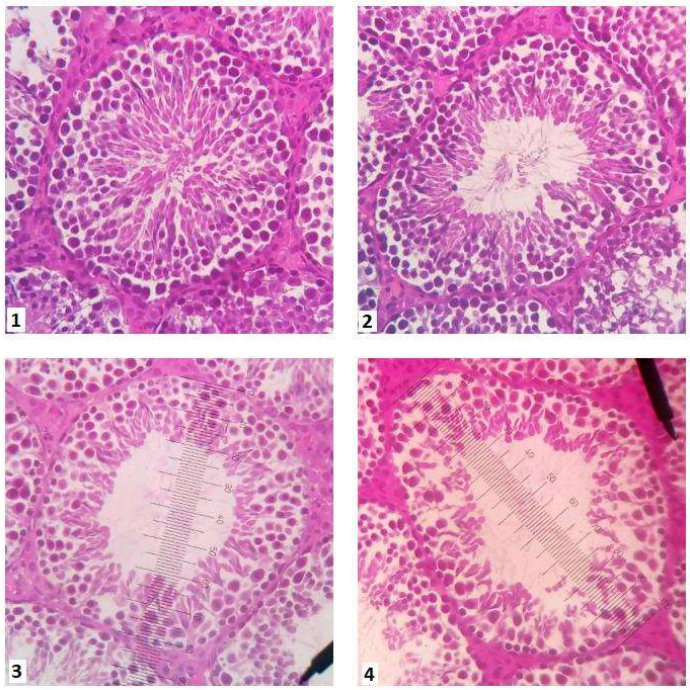

Figure 1: Micrographs (400x) of cross section of seminiferous tubules of mice treated with papaya seeds extract: 1) Control group; 2) 2 mg/40 g; 3) 4 mg/40 g; 4) 8 mg/40 g body weight.

4. Discussion

The data in Tables 1 and 2 as well as the photographs in Fig.1 clearly imply that the papaya seeds extract has anti-spermatogenic activity. Phytochemical screening studies showed that papaya seeds are rich in alkaloids, tannins, saponins, phenols, terpenoid, flavonoid and sterol [6-8]. There are many studies that confirm the antifertility effects of chemical compounds similar to those of papaya seeds. *Citrullus colocynthis* is revealed to contain flavonoids, saponins and steroid [9]. Methanolic extract of this plant is suggested to have contraceptive properties because proven to decrease in testicular weight, sperm concentration, level of testosterone, LH and FSH, in addition to cause impairment of spermatogenesis in rats [10]. Another plant species that also indicates antifertility properties is *Chenopodium album*. In rats treated with this plant seeds extract is known to induce instantaneous immobilization of spermatozoa allegedly due to disintegration of plasma membrane and dissolution of acrosomal cap [11]. This plant, as indicated, also contained chemicals similar to papaya seeds extract mainly flavonoids [12].

How flavonoids can affect spermatogenesis? Apparently, these substances have inhibitory activity on aromatase, an enzyme that plays an important role in catalyzing the conversion of androgens into estrogens. Due to inhibition of the enzymes, testosterone levels increase and affect pituitary function via a negative feedback mechanism so that the secretion of FSH and LH is suppressed that lead to inhibition of spermatogenesis [13]. Saponin is another instance of phytochemicals that also contained in papaya seeds extract. Saponins, mainly steroids and triterpenoids, allegedly also give effects on the hypothalamus-pituitary-testis axis in laboratory mammals that potentially lead to decrease spermatocyte and spermatid counts [14].

Data in Table 2 and Fig.1 clearly showed that papaya seeds extract affect diameter and epithelial thickness of seminiferous tubules of testis. These phenomena may also associate with function of the hypothalamus-pituitary-testis axis. Decreases in GnRH and gonadotropin (FSH and LH) will inhibit the process of spermatogenesis due to degeneration of the seminiferous tubules resulting in decreased diamater and epithelial thickness of the tubules [15].

Although significantly affecting the process of spermatogenesis, papaya seed extract did not show any significant change in the number of spermatogonia. This may be related to the testicular immune properties, especially spermatogonial stem cells, which are less sensitive to injury, capable of self-renewal [16-17].

5. **Conclusion**

Given proven capable of reducing the number of spermatocyte and spermatid cells and reducing the diameter and epithelial thickness of seminiferous tubules of mice testes, it can be infered that papaya seeds extract can be used as anti fertility agent.

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