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# A review on the antifertility potential of C*arica papaya l.* Seed extract as male contraceptive

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## Abstract

The rising prevalence of unintended pregnancies represent a serious global issue with wide-ranging consequences. Despite the broad use of female contraceptives, their side effects and long-term risks point to the need for safer male contraceptives options. This systematic review evaluates the antifertility potential of *Carica papaya* L. seed extract as a male contraceptive. A comprehensive search of PubMed, Scopus, and Google Scholar was conducted to identify studies examining the effects of *Carica papaya* L. seeds or seed extracts on male fertility. Eligible studies reported outcomes including sperm count, motility, morphology, fertility indices, and histopathological changes. The evidence shows that *C. papaya* seed extracts particularly the chloroform and benzene fractions, as well as bioactive constituents such as alkaloids (carpaine, pseudocarpaine, 1,2,3,4-tetrahydropyridin-3-yl-octanoate), and benzyl isothiocyanate (BITC) can produce significant effects on the male reproductive system across multiple experimental models. These effects were dose- and duration-dependent and primarily reversible upon treatment withdrawal. Toxicological evaluations showed minimal toxicity, normal body and organ weights, and no genototoxic effects. *Carica papaya* L. seed extracts demonstrate strong antifertility effects by impairing sperm motility, viability, count, morphology, and fertility, while remaining largely non-toxic. The effects are mostly reversible, making it a promising natural male contraceptive candidate. However, further research, including human clinical trials, long-term safety studies, and detailed mechanism investigation are needed to validate efficacy and safety.

**Keywords:** *Carica papaya* Seed Extract; Male Contraceptive; Antifertility; Spermatogenesis inhibition; Benzyl isothiocyanate (BITC)

## 1. Introduction

The conversation surrounding contraceptive access and acceptance becomes increasingly urgent as unintended pregnancies continue to rise. Between 2015 to 2019, unintended pregnancies averaged 121 million per year globally, with the Philippines reporting at 51% of all pregnancies [1, 2]. These have been linked to adverse maternal and infant health outcomes, including post-partum depression, unsafe abortions, substance abuse, and various pregnancy complications [3, 4, 5] Hence, access to effective contraceptive methods play a crucial role in decreasing likelihood of pregnancies and help address global health repercussions relating to this. While contraceptive use among women is generally well-accepted, studies by Khan (2001); Otte et al. (2023); & Groene et al. (2025) highlight that significant gaps persist, particularly concerns related to side effects [6, 7, 8].

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Traditional reversible oral contraceptives have been the mainstay given that some women still want a choice to get pregnant later on in their lives while some women cannot tolerate injectables or implants. The most significant benefit is the reduced risk of pregnancy, but side effects still pose to many women. It is often associated with menstrual bleeding irregularities, edema, mood changes, and nausea [9, 10]. In addition, long-term use has been associated with more severe risks, including increased cardiovascular complications, hormonal and metabolic changes, and higher risk for breast and cervical cancer [9, 10]**.** These adverse effects have driven ongoing research and innovation to develop male contraceptives, aiming to provide safer and more balanced alternatives that share the responsibility for contraception while minimizing health risks for women.

At present, the only available forms of male contraceptions are condoms and vasectomy. Condoms are the oldest and widely used contraceptive, but not ideal because of its high failure rate. Amory et al. (2016) & Khourdaji et al. (2018) reports that condoms have an estimated failure rate of 15-18% with regular use, and long-term use is low with about 57% of men discontinuing use within the first use [11, 12]. On the other hand, vasectomies are invasive and have complications of their own. As a result, researchers have focused and shifted on understanding the effectiveness of herbal medicines as contraceptives and one of which is *Carica papaya* L.

*Carica papaya* L. is a multi-faced plant that has anti-oxidant, antibacterial, anti-inflammatory, and antihypertensive properties. While it is primarily valued for its various medicinal properties, growing evidence has highlighted its potential antifertility effects, particularly from its seed. Studies have shown that *Carica papaya* seed extracts contain bioactive compounds capable of altering sperm production, motility, and morphology, indicating their potential as a natural male contraceptive. This makes papaya a viable alternative to conventional hormonal contraceptives, offering a plant-based option that is cost-effective, non-toxic, and orally bioactive. Thus, this study aims to review the antifertility potential of *Carica papaya* L. seed extract as a male contraceptive by gathering literatures that assess the antifertility activity in *Carica papaya* L.

## 2. Methodology

This systematic review aimed to evaluate the antifertility activity of *Carica papaya* L. seed extracts in male studies. The review examines studies on the phytochemical profile, pharmacological activities, and antifertility mechanisms of Carica papaya L. seed extract in male subjects. Moreover, a comprehensive search was conducted in major databases such as PubMed, Scopus, and Google Scholar using keywords "*Carica papaya* L., seed/seed extract, antifertility, male contraceptive, azoospermia, and spermatozoa". However, the study is limited by the availability of published data; hence, no limit to publication year is set. Eligible studies that specifically evaluated the contraceptive aspect of the plant were subjected to data extraction. The inclusion criteria emphasized peer-reviewed studies that:

- Used *Carica papaya* L. seeds or seed-derived extracts as the primary treatment.
- Identified, analyzed, or reported the phytochemical composition or bioactive compounds present in the seed or seed extract.
- Reported at least one antifertility-related endpoint, such as sperm parameters, testicular or epididymal histopathology, fertility outcomes, and the like, on male subjects.

Studies excluded were those focused exclusively on other plant parts (e.g., leaf, stem, or roots) or mixed plant formulations, and focused only on female fertility or non-reproductive outcomes.

## 3. Review of related literature

### 3.1. Botanical Description and Distribution

*Carica papaya Linn*, commonly known as Papaya or Pawpaw, is a tall, single-stemmed fruit tree belonging to the *Caricaceae* family. It is native to Central America and Southern Mexico, and now widely cultivated across tropical and subtropical regions, such as Southeast Asia, Australia, Africa, the Caribbean, the Philippines, and many more [13]. The widespread distribution and year-round availability of *C. papaya* support its accessibility for continued medicinal and scientific exploration.

The plant grows 20-30 feet tall with a hollow green to tan stem, large palmately lobed leaves, and fruits that vary in shape, size, and ripening color. And of particular importance is its seeds that comprise about 20% of the fresh fruit weight and are typically round to ovoid, enclosed in a fibrous outer coating that darkens from white to black as the fruit ripens. These seeds possess a distinct internal structure and are rich in bioactive compounds, making them an important

subject for continued medicinal and scientific investigation, contributing to their growing pharmacological relevance [14, 15, 16, 17].

### 3.2. Antifertility Compounds found in Carica papaya L. Seed Extract

#### *3.2.1. Alkaloids*

Alkaloids are naturally occurring plant-derived compounds characterized by their nitrogen-containing structures and wide structural diversity. They are known for their various biological activities, ranging from medicinal effects to toxic properties.

Preliminary studies of Govindochari et al. (1965). confirmed the presence of alkaloids carpaine and pseudocarpaine in *C. papaya*. However, further studies identified the presence of 1,2,3,4-tetrahydropyridin-3-yl-octanoate obtained from *C. papaya* ethyl acetate extract [18, 19]. It was isolated using solvent partitioning followed by column chromatography. IR analysis indicated the presence of N-H, ester C=O, aliphatic C-H, C=C, and C-O functional groups. And NMR spectroscopy confirmed its molecular formula as C13H23NO2, corresponding to three degrees of unsaturation. While $^{13}$C-NMR and DEPT analysis indicated the presence of a carbonyl group, two double-bonded carbons, an oxygenated methine, one methyl group, and eight aliphatic methylene carbons. HMQC and HMBC correlations supported the connectivity of the ester, double bond, and secondary amine groups. Consequently, its structure showed similarities to the monomer of carpaine.

Moreover, at a concentration of 12.5 ng/mcL, 1,2,3,4-tetrahydropyridin-3-yl-octanoate was able to decrease sperm motility and viability, and increase sperm abnormalities of rats [20].

#### *3.2.2. Benzyl Isothiocyanate (BITC)*

Benzyl isothiocyanate (BITC) is a bioactive phytochemical present in various cruciferous plants and is particularly concentrated in *C. papaya* seeds. It is formed via the enzymatic hydrolysis of glucotropaeolin by myrosinase producing an unstable intermediate. Additionally, Barroso et al. (2016) reported that BITC yield is enhanced when extracted using supercritical $CO_2$ at 80°C and 200 bar [21].

Systematic reviews have highlighted BITC in *C. papaya* seeds for its antihelminthic and anticancer properties [15**,** 22]. However, Udoh (1999) demonstrated its antifertility effects in rats, showing degeneration of the germinal epithelium, reduction of Leydig cells, and formation of vacuoles showing its promising antifertility effects [23, 24].

**Table 1** Summary of Key Antifertility Compounds Found in *Carica papaya* L. Seeds

| Compound | Chemical Class | Extraction Method | Notable Properties | Reference |
|---|---|---|---|---|
| 1,2,3,4-tetrahydropyridin-3-yl-octanoate | Alkaloid-like ester | Ethyl acetate extraction → solvent partition → column chromatography | Structurally related to carpaine | [20] |
| Benzyl isothiocyanate (BITC) | Isothiocyanate | Supercritical $CO_2$ at 80 °C / 200 bar | Oil yield maximized at 80 °C / 200 bar (2.56 %); 40 °C / 200 bar gave 1.33 %. | [21] |
| Benzyl isothiocyanate (BITC) | Isothiocyanate | Oven dried & pulverized → Dissolved in fresh palm oil | Oxidative stress-mediated disruption of spermatogenesis | [23, 24] |

### 3.3. Antifertility Activity of *Carica papaya* L. Seed Extract

The seed extract of *Carica papaya* L. has demonstrated contraceptive effects among different male species such as rats, mice, rabbits, and monkeys. However, it exhibited that response depends on dose, duration, route of administration, and extract used. Table 2 summarizes the antifertility activity of representative studies detailing materials used and corresponding antifertility outcomes observed in *C. papaya.*

Preliminary studies showed that the antifertility effects in rats and mice were primarily post-testicular, marked by reduced cauda epididymal sperm count and impaired motility [25, 26, 27, 31]. Rabbits and langur monkeys, on the other hand, showed more visible testicular consequences, like severe oligospermia and even azoospermia. [29, 30].

Among the crude extracts, Chloroform showed the greatest activity whereas extract polarity increased with contraceptive efficiency. In rats, the chloroform extract caused complete suppression of sperm motility within 20 days, while rabbits and langur monkeys developed severe oligospermia to uniform azoospermia after 60–120 days of treatment [25, 29, 30]. Further purification identified the benzene fraction of the chloroform extract as a highly active component, producing total inhibition of sperm motility in rats after 60 days [31, 32] and achieving uniform motility suppression in langur monkeys within the same time period [33]. Comparable outcomes were observed in rats treated with the methanol subfractions of the benzene fraction [34, 35]. While, the thin-layer chromatography of this subfraction further isolated MCP I and ECP I, also induced complete sperm motility inhibition in rats after 90 days [36]. These findings were accompanied by declines in sperm concentration, count, and viability, as well as increased morphological abnormalities.

Although, notably, there were no contraceptive or toxic effects in rabbits with the use of aqueous seed extract, indicating possible species difference or insufficient extract potency [37].

*3.3.1. Ultrastructural Changes*

In the study by Pathak et al. (2000), it was found that rats treated with benzene fraction of the chloroform seed extract for 150 days largely retained normal testicular and epididymal histology. with only slight and scattered abnormalities [31]. A few of seminiferous tubules showed disorganized germ cells and lack of mature sperm, while some epididymal epithelial cells displayed mild vacuolization and pyknotic nuclei. In contrast, Lohiya et al. (2005) and Manivannan et al. (2009) observed more pronounced disruption of spermatogenesis after 360 days of exposure to MCP I, ECP I, and the benzene fraction [35, 36]. In these treated animals, most seminiferous tubules showed epithelial injury, with Sertoli cell vacuolization and germ cells exhibiting nuclear pyknosis and cytoplasmic vacuoles. Spermatid maturation was particularly impaired. The tubule lumens contained germ-cell debris and fewer spermatozoa, although Leydig cells remained unaffected. Similar patterns were also reported in rabbits treated with chloroform fractionand in langur monkeys exposed to the benzene fraction for 360 days [29, 33]. Notably, the unchanged epididymal histology suggests that the main antifertility effect may be directed at the spermatozoa rather than the epididymal environment.

**Table 2** Summary of Male Antifertility Effects of *Carica papaya L.* Seed Extract

| **Extract** | **Model** | **Result** | **Reference** |
|---|---|---|---|
| Ethanol | Rats | D3, D4, D5 | [25] |
| Aqueous | Rats, Mice | D3, D5 | [26, 27] |
| | Rabbits | N | [37] |
| Chloroform | Rabbits, Monkeys | A, D1, D2, D3, I1 | [29, 30] |
| Benzene fraction of chloroform extract | Rats | D1, D2, D3, D5, I1, T | [31] |
| | Monkeys | A, D1, D2, D3, D4 I1, T | [33] |
| MSF of benzene fraction of chloroform extract | Rats | D1, D2, D3, D5, I1, T | [34, 35] |
| MCP I & ECP I | Rats | D1, D2, D3, D5, I1, T | [36] |

**Legends:** [A] Azoospermia | [D1] Decrease in sperm concentration (sperm/mL in semen) | [D3] Decrease in sperm motility | [D2] Decrease in sperm viability | [D4] Decrease in *testicular* sperm count | [D5] Decrease in *cauda epididymal* sperm count | [I1] Increase in sperm sperm abnormalities/morphology (or percent abnormal spermatozoa) | [N] No changes at all | [T] Total inhibition of sperm motility

### 3.4. Safety and Toxicity

Earlier sections discussed the effects of *Carica papaya L.* seed extract on sperm parameters and the histological features of male reproductive organs. A common finding among the studies was that its contraceptive effect was reversible,since the altered sperm and tissue parameters were observed to return to normal after the treatment was stopped.This was also seen in the studies reported by Goyal et al. (2010) and Manivannan et al. (2009), who reported that long-term administration of the methanol subfraction in rats caused no permanent reproductive alterations upon treatment

discontinuation [34, 35]. Likewise, Lohiya et al. (1999, 2002, & 2008) documented complete recovery from azoospermia in rabbits and langur monkeys despite prolonged exposure to the chloroform extract [29, 30, 33].

The safety of the extract was also supported by other findings, including unchanged body and organ weights, normal tissue biochemistry, and the absence of remarkable toxicological findings. These results suggest that the extract remains clinically tolerable. While the toxicity studies showed that both a single dose of 2000 mg/kg bw MSF and repeated administration for 28 to 90 days at doses reaching up to ten times the contraceptive level produced no adverse effects in rats [38]. Moreover, the methanol subfraction consistently showed a non-toxic profile even during long-term administration with no observed systemic, behavioral, physiological, or histological disturbances involving vital organs or metabolic activity.

The same result was observed in genotoxicity studies. Ansari et al. (2011a) found that markers of chromosomal damage, such as fragments, dicentrics, rings, and exchanges, were not significantly different from the negative controls in rats and rabbits [39]. In another study, treatment with 1000 mg/kg bw MSF for five days resulted in a dominant lethal index of 0% [40]. (Ansari et al., 2011b). Although higher doses of the methanol subfraction were able to induce infertility in rats, no evidence of developmental toxicity or teratogenicity was reported [41]. Overall, these findings strongly support the favorable safety profile of *Carica papaya L*. seed extract and its potential as a male contraceptive candidate.

**Table 3** Summary of Safety and Toxicological Outcomes *Carica papaya* L. Seed Extracts in Male Models

| Parameter | Model | Key Finding/s | Reference |
|---|---|---|---|
| Long-term administration | Rabbits | Chloroform extract at 20 & 50 mg/animal for 150 d induced reversible contraception | [29] |
| | Rats | No changes in the subcellular characteristics | [32] |
| | Monkeys | Chloroform extract & its benzene fraction at 50 mg/kg for 360 d induced reversible azoospermia | [30, 33] |
| | Rats | Long-term (360 d) oral administration of MSF at 50 mg/kg caused no overt general toxicity | [35] |
| | Rats | Oral administration of MSF at various doses for 364 d caused no significant changes | [34] |
| Acute toxicity | Rats | Single high dose (2000 mg/kg) caused no systemic toxicity; only short-term observations | [38] |
| Sub-chronic toxicity | Rats | Repeated daily doses (50–500 mg/kg) over 28 or 90 days caused no systemic toxicity | [38] |
| Genotoxicity | Rats & Rabbits | No significant chromosomal aberrations | [39] |
| | Rats & Rabbits | Did not induce heritable genetic damage | [41] |
| Developmental toxicity & Teratogenicity | Rats | No developmental toxicity and teratogenicity | [39] |

## 4. Conclusion

The increase in unintended pregnancies highlights the importance of developing contraceptive methods that are both effective and safe. While most currently available options are only for women, the side effects and possible health risks linked to these methods show the importance of exploring male-directed alternatives.

Based on the studies reviewed, the seeds of *Carica papaya L.* contain bioactive compounds such as alkaloids and benzyl isothiocyanate (BITC), which are associated with decreased sperm motility and count, along with increased sperm abnormalities. An important finding across the included studies is that these changes were generally reversible after withdrawal of the extract and do not cause significant toxicity.

Despite these promising findings, some limitations remain because most of the currently available evidence is derived only from animal studies, and there is still a lack of human clinical trials to confirm both efficacy and safety in actual use. Also, the exact mechanisms by which the extract affects sperm function are not yet fully understood, and long-term data about reproductive safety, toxicity, and possible effects on future offspring remain limited.

Overall, *Carica papaya L.,* a widely cultivated tropical plant known for its nutritional and medicinal value, presents significant promise as a natural source for the development of a safer male contraceptive. But continued research may help establish its role as a practical and effective alternative in male reproductive health.

## Compliance with ethical standards

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### *Disclosure of conflict of interest*

The authors have no conflict of interest(s) to declare.

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