Anti-fertility Potential of *Carica papaya L.* (Pawpaw) in Males

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Abstract: The use of herbal contraceptives in males as an alternative to traditional contraceptives is an increasing method of preventing unintended pregnancies in women. To prevent adverse effects of contraceptives in women such as amenorrhea, bleeding, and vaginal pain, alternative male contraceptives are recommended. This review discussed the various compounds in the *Carica papaya* L. (*C. papaya*) plant that have antifertility properties and characterized the effects of its various parts, such as the seeds, leaves, stems, fruit pulps, and roots, on the testes, spermatozoa, sperm motility, sperm morphology, seminiferous tubules, and testosterone levels of male rodents. Reliable search engines such as Web of Science, SCOPUS, Google Scholar, and PubMed were used to find relevant articles for the review. The paper had no date of publication range and only used studies that evaluated the contraceptive aspect of C. *papaya.* The seeds, leaves, stems, roots, and fruit pulps of the papaya were found to have antifertility properties. The papaya seeds were the most studied in the aspect of fertility. The *C. papaya* L. was found to have various effects such as testes inflammation, destruction of seminiferous tubules, abnormal sperm morphology, low sperm motility, and low testosterone levels, which reduce fertility rate, sperm production, etc. Overall, *C. papaya* L. has antifertility properties and the potential to work as a male contraceptive.

Keywords: *Carica papaya* L.; male contraceptive; antifertility; medicinal plant; herbal contraceptive

1. INTRODUCTION

1.1. Background of the Study

With the rise of unintended pregnancies worldwide, contraceptives are portrayed as an effective intervention that can improve handling problems ranging from HIV/AIDS to unintended pregnancies (Senderowicz, 2020). Contraception refers to using various devices, drugs, or procedures to intervene with pregnancy. Effective contraceptives aid with the prevailing global health discourse of overpopulation by allowing people to engage in a physical relationship that ensures them the freedom to choose whether or not to have children. A report from 2013 estimated that 99% of women engaging in sexual intercourse used at least one kind of contraceptive in their life, while approximately 88% of sexually active women not seeking pregnancy were reported using contraceptives at any given time (Kavanaugh & Pliskin, 2020; Teal & Edelman, 2021). Additionally, long-acting reversible contraceptives like same-day insertions can reduce teen births to 82% and abortion cases to 71% (Yi et al., 2022). With contraceptives, decreasing rates of unintended pregnancies would be evident, along with reducing the adverse health repercussions seen in mothers and infants (Dehingia et al., 2019).

The most significant benefit that female contraceptive use has shown towards health comes from the reduction of pregnancies that pose a great risk to maternal, perinatal, and infant survival (Cleland et al., 2012). With that, women use traditional contraception like vaginal rings, pills, patches, and implants, which induces adverse effects on the woman's health like irregular and heavy bleeding, amenorrhea, pain in the vagina, and pain in the lower libido (Rossier & Corker, 2017; Bellizzi et al., 2020). Given that some women cannot use contraceptive methods due to the side effects that contraceptives possess, the demand for male contraceptives is needed and evident. Evident bias towards female contraceptives is seen, wherein female contraceptives consist of nine methods, and male contraception merely consists of two methods— vasectomy and condoms. Abbe et al. (2020) reported that the ultimate availability of male contraceptives is a step toward advancing reproductive justice and immense equity in family planning, efficiently decreasing global unintended pregnancies.

To counter the adverse effects of contraceptives and provide accessible contraceptives to women, individuals have been seeking to utilize herbal medicine as an alternative to chemical-based contraceptives as it has lesser repercussions and is more inexpensive (Nyeko et al., 2016; Ansari et al., 2017). For the past decades, researchers have focused on understanding herbal medicines' effectiveness as a form of treatment— *Carica papaya* L. (Pawpaw) being one of the herbal medicines. *Carica papaya* L. is a medicinal plant that has biomedical properties that can treat ailments such as but not limited to inflammation, diabetes, hypertension, and antifertility (Dotto & Abihudi, 2021). Various extracts of *Carica papaya* from different parts of the plant, such as seed extract and root extract, have shown contraceptive activities in male and female rodents (Nwaehujor et al., 2019). Researchers used various parts of the papaya plants as an antifertility agent that has shown substantial potential in searching for a safer, less expensive, and alternative technique for regulating fertility in male animal models. With that established, this paper aims to review the pharmacognostic analysis of the antifertility property of *Carica papaya* L. as a male contraceptive by gathering related studies that assess the antifertility characteristics of the *C. papaya* plant in male rodents.

2. METHODOLOGY

The research paper conducted a systematic literature review (SLR) by obtaining articles related to the research topic. The following inclusion criteria were used to narrow down the articles related to *C. papaya* L. There was no limit to publication years due to the limited studies on *C. papaya* L. The language of the research articles was in English. Papers that discussed and experimented on the stems, seeds, leaves, fruit pulps, and roots of *C. Papaya* L. and evaluated their contraceptive aspect were included. The articles used in this paper studied male animal models and observed the following: testes, seminiferous tubules, spermatozoa, sperm morphology, sperm motility, and testosterone levels. The studies that did not meet the mentioned inclusion criteria above were automatically excluded. Using the inclusion criteria, the paper was able to gather forty-one (41) studies for the literature review.

The paper used the following search engines: Web of Science, SCOPUS, Google Scholar, and PubMed. All of the mentioned search engines contain peer-reviewed journals and the most credible sources since peer-reviewed papers are reliable sources of information due to the checked and analyzed content by other researchers (Riley & Jones, 2016). To search for the relevant papers, the following keywords were used: antifertility, *Carica papaya* L*.,* leaves, pulp, rodents, roots, seeds, seminiferous tubules, spermatozoa, sperm morphology, sperm motility, stem, testosterone levels, and testes.

3. RESULTS AND DISCUSSION

3.1. Antifertility compounds found in *Carica papaya* L.

3.1.a. Alkaloids

Alkaloids are among the abundant secondary metabolites in many plants (Amirkia & Heinrich, 2014). These metabolites may either be colorless crystals depending on the temperatures of the surroundings, or they can also be colored. Its chemical structure contains mostly basic nitrogen atoms but can also contain hydrogen, oxygen, and carbon (Singh & Sharma, 2018). Some detected alkaloids in the papaya leaves are carpaine, pseudocarpain, and dehydrocarpaine I and II. Carpaine is the major alkaloid found in the leaves and the bark of *C. papaya,* which can inhibit fertility. Pseudocarpain are new compounds found in the leaves which are white needle-like crystals in appearance (Khuzhaev & Aripova, 2000). Pseudocarpain was discovered to be a stereoisomer found in *C. papaya* in small quantities. The fragmentation patterns of pseudocarpain are similar to those of carpaine; therefore, the two (2) alkaloids must have similar chemical gross structures. Tang (1979) found dehydrocarpaine I and II compounds in the leaves of *C. papaya* through the thin layer chromatography (TLC) method, a technique used to identify specific compounds present, their purity, and their purity reaction. Although the presence of pseudocarpain and dehydrocarpaine I and II compounds were detected in the papaya leaves, there has not been any study indicating that these compounds affect antifertility since there is a possibility that some quantities of these compounds may be lost during extraction (Govindachari et al., 1954; Govindachari et al., 1965; Khuzhaev & Aripova, 2000; Lohiya et al., 2000; Santiago & Strobel, 2013; Wang et al., 2015).

3.1.b. 1,2,3,4-tetrahydropyridin-3-yl octanoate

1,2,3,4-tetrahydropyridin-3-yl octanoate is classified as a type of alkaloid obtained from the *Carica papaya* L. seeds through ethyl acetate extraction. From the extraction, the compound was isolated through solvent partition and column chromatography. From the extract, 26.1 mg of a colorless solid was not fluorescent in the presence of ultraviolet light (UV) light. The molecular formula of the compound is $C_{13}H_{23}NO_2$; however, it must be noted that the molecular formula provided in the paper does not match with 1,2,3,4-tetrahydropyridin-3-yl octanoate when searched online. The compound has the potential for antifertility, given that it decreased factors that led to fertility at a concentration of 12.5 ng/µL. Additionally, extracts created with methanol and ethyl acetate can be used, inhibiting the testes' spermatogenesis process, which is a sign of anti-fertility. The compound was recently discovered, which limits the resources related to the compound (Julaeha et al., 2015; Dotto & Abihudi, 2021).

3.1.c. Benzyl isothiocyanate (BITC)

Benzyl isothiocyanate (BITC) is an anthelmintic and antibacterial compound found in the leaves, roots, and stems, but mostly in the seeds (Kermanshai et al., 2001; Nakamura et al., 2007; American Chemical Society Chemistry for Life, 2019; Hans et al., 2019). BITC occurs when the myrosinase enzyme catalyzes in papaya seeds (Habtemariam, 2019). A superstitial carbon dioxide extraction system is needed to extract the compound to isolate the BITC in the oil from the seeds (Barroso et al., 2016). The activity of the myrosinase enzyme was found to be high in the *C. papaya* seeds, and benzyl-glucosinolate levels were also high in the seeds, fruit skin, and pulp.

A study conducted by Adebiyi et al. (2003) utilized *C. papaya* seeds extracted with 80% ethanolic extract of papaya seeds (EEPS) that caused tocolysis of uterine strips isolated from pregnant and non-pregnant rats, resulting in a weak uterus recovery and toxic effects to the uterus tissues that caused irreversible effects in the myometrium (Okonkwo Omeje et al., 2020) (Adebiyi et al., 2003). Moreover, a study by Udoh, P., & Kehinde, A. (1999) experimented on male albino rats to determine the effects of BITC on the reproductive organs. The results showed degradation of germinal epithelium, Leydig cells, and vacuoles in the tubules.

3.2. Effects of the different parts of *Carica papaya* L. in male fertility.

3.2.a. Seeds

The seeds found in the *C. papaya* L. fruit have been found to have antifertility effects and have the potential to be used as a male contraceptive. It has been noted that papaya seeds can be used for antifertility because of a compound called benzyl isothiocyanate (BITC). Additionally, the seeds are usually made into extracts and produce results with variable responses based on the duration of a specific experiment, dosage given to the test subjects, and way of administration to the laboratory animals (Lohiya et al., 2005; Abdulazeez & Sani, 2011; Kyei-Barffour, 2021). Studies from Lohiya & Goyal (1992), Verma et al. (2006), and Manivannanan et al. (2009) discussed the papaya seeds, wherein all three papers used different extraction methods like crude chloroform extract, aqueous *C. papaya* extract, and chloroform benzene methanol subfraction (MSF). All papers concluded that the papaya seeds are safe and could be used for antifertility; given that sperm abnormalities were noted, there was a decrease in sperm motility and viability, which are factors leading to antifertility.

3.2.b. Leaves

The leaves of *Carica Papaya* are known for various therapeutical and nutraceutical properties. Multiple studies have proven that papaya leaves are rich in compounds such as alkaloids (carpaine and pseudocarpaine), phenolic compounds (ferulic acid and chlorogenic acid), flavonoids (kaempferol and myricetin), carotenoids (β- carotene), and lycopene— which gives the leaves pharmacological qualities such as anti-tumor, anti-inflammatory, abortifacient, and anti-infertility. In recognition of the numerous medical benefits of papaya leaves, various researchers performed studies using papaya as a medicinal herb that can aid thousands of people with their ailments (Yogiraj et al., 2014; James et al., 2018). Studies conducted by Oyekunle & Omope (2010) and Airaodion et al. (2019) used an aqueous extract of *C. papaya* leaf to determine its efficacy as a male contraceptive. Oyekunle & Omope (2010) used eighteen (18) rats divided into two groups, a control group and a test group. The control groups were given 0.9% physiological saline for 21 days, while the test group was administered 500 mg/kg body weight single dose of the extract. On the other hand, Airaodion et al. (2019) used thirty (30) rats and grouped them into six (6). Groups A, B, and C were orally given normal saline for 10, 20, and 30 days, respectively, whereas groups D, E, and F were given 500 mg/kg body weight of papaya ethanolic leaf extract. Both studies showed results that signified a significant reduction in sperm viability, sperm count, sperm motility, and normal sperm morphology. Additionally, Oyekunle & Omope (2010) reported lesions on the degenerating seminiferous tubule and a disturbance in the interstitial cells of the testis, whereas Airaodion et al. (2019) reinforced the report by speculating that the leaves contain a chemical called papain which may penetrate the blood-testes barrier and cause adverse effects on the seminiferous tubules.

3.2.c. Stem

The *C. papaya* stem of the papaya plant consists of nutrients and phytochemicals such as carbohydrates, protein, vitamin C, niacin, alkaloids, tannins, and steroids. The papaya stem also contains minerals like magnesium, calcium, phosphorus, sodium, and zinc (Chinwendu et al., 2013). Although the stem of the *C. papaya* contains valuable nutrients, only the outer layer of its stem, called bark, was studied. Studies from Okanlawon et al. (2010) and Kusemiju et al. (2010) researched the effects of the aqueous extract of the *C. papaya* bark. Both studies exhibited results of histological alterations in the seminiferous tubules of the rats, such as deformation and degeneration. Additionally, a significant reduction in sperm count and motility was seen, and there was no substantial reversal of antispermatogenic effects. Overall, the bark extract of *C. papaya* can affect the testes and seminiferous tubules; therefore, further research on the extract must be done to validate its effect on fertility.

3.2.d. Roots

The roots of *C. papaya* contain cyanogenic glucosides, which can form cyanide compounds. Cyanide concentrations were higher in the tap roots of the *C. papaya*, where cyanogenic glucoside is continually regulated (Bennett et al., 1997; Gleadow & Møller, 2014). An experiment on cyanide toxicity in male albino rats revealed that exposure to cyanide could cause a significant change in the reproductive organ weight, sperm motility, sperm count, sperm abnormality, FSH and LH, and testosterone levels (National Toxicology Program, 1993; Shivanoor & David, 2014).

Moreover, Nwaehujor et al. (2019) investigated the effects of *C. papaya* root extracts on the fertility of male Wistar rats using 80% methanol and found no mortality at 2000 mg/kg dose in acute toxicity, but induced diuresis symptoms were observed. There was a reduction in sperm count and an increase in defective sperm. There were increasing levels of aspartate aminotransferase and blood urea nitrogen, mild kidney and cardiac hyperemia, hepatic degeneration, and necrosis of the germinal epithelium of the testes. The study suggested caution upon using *C. papaya* root extracts in treating diseases and contraception.

3.2.e. Pulp of the Fruit

The pulp of the *C. papaya* L. contains vitamins A, C, and E, along with minerals such as magnesium and potassium. It also contains vitamin B complexes such as pantothenic acid and folate, and dietary fibers (Santana et al., 2019). Furthermore, results obtained from the Phytochemical analysis in the study of Asuquo et al. (2020) showed that *C. papaya* ripe fruit ethanolic extract contains saponins, cardiac glycoside, flavonoid, deoxy-sugar, terpenes and steroids, phlobatannins, alkaloids, anthraquinone, and carbohydrates. The presence of alkaloids and flavonoids could be the possible cause of antifertility due to their constituents.

In a study by Asuquo et al. (2020), an investigation was conducted to see the hormonal and reproductive effects of *C. papaya* ripe fruit on Wistar rats in an alcohol-experimental approach. The flesh part of the papaya fruit was blended in a blender to obtain the pulp and mixed with 0% ethanol for 72 hours. After which, the extract was placed in a water bath at 45-60°C, producing the extract. The rats were divided into six (6) controlled groups with different ethanol concentrations. Moreover, the results showed that the extract reduced the sperm count, motility, and luteinizing hormone in the Wistar rats. However, the concentration greatly increased the testosterone level (Asuquo et al., 2020). Furthermore, group 2 showed spermatogenic cell distortions, which cause damage to the sperm cell (Asuquo et al., 2020).

4. CONCLUSIONS

The seeds, leaves, stems, fruit pulps, and roots of the *Carica papaya* L. plant were found to have antifertility effects in male rodents. The extracts of *C. papaya* resulted in sperm abnormalities, low testosterone levels, low fertility rate, and low sperm production. In general, *C. papaya* has the potential to be used as an alternative herbal male contraceptive; however, it is recommended to perform more thorough studies to identify the effects of its antifertility compounds in male humans and other animal models.

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