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Papainic Control: Redefining Birth Regulation through Papaya Seed Bioactive

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ABSTRACT

Birth control pills (BCPs), also called oral contraceptive pills (OCPs), have gained widespread use globally. Since 1994, an estimated 151 million individuals have been reported as OCP users, with over 20% of people of reproductive age in 27 countries using them. OCPs are not only prescribed for preventing unintended pregnancies but also for managing conditions such as menstrual irregularities, endometriosis, and polycystic ovarian syndrome (PCOS). Moreover, research indicates that these pills may reduce the risk of developing ovarian and endometrial cancers. Despite these benefits, the decision to use OCPs should be made carefully, as certain groups of users have been observed to face a higher risk of hypertension, cardiovascular diseases (CVD), cancer, and venous thromboembolism. The growing need for safe, effective, and affordable contraceptive options has encouraged interest in plant-derived alternatives. This study investigates the potential of *Carica papaya* (papaya) seeds as a natural source for developing male contraceptive agents. Papaya seeds contain several bioactive phytochemicals, including alkaloids, flavonoids, and saponins, which have demonstrated anti-fertility effects in animal models. Scientific studies suggest that papaya seed extracts can notably decrease sperm count, motility, and viability, while showing minimal long-term toxicity or hormonal disruption. This review highlights the available evidence on the contraceptive potential of papaya seed extracts, their mechanisms of action, dosage optimization, and fertility recovery following treatment withdrawal. The findings indicate a promising avenue for creating a non-hormonal, plant-based male contraceptive, contributing to advancements in family and reproductive health. Further clinical investigations are necessary to confirm the safety, efficacy, and formulation. Parameters for women Ethnopharmacological relevance: Traditionally, *Carica papaya* seeds have been used by healers as a natural remedy for various ailments and as a male contraceptive, as well as for inducing abortion in women.

Keywords: Contraception, Fertility control, Polycystic Ovary Syndrome (PCOS), Endometrial carcinoma, Cardiovascular disorders.

INTRODUCTION:

Birth Control and Contraceptive Methods

Contraception refers to the practice of preventing pregnancy through various means such as devices, medications, surgical procedures, or behavioral methods. It enables women to make informed decisions regarding their reproductive health and family planning. Modern contraceptive technologies aim to regulate fertility through medical and technological innovations. Over the 20th century, significant advancements have been achieved in women's reproductive health, leading to safer, more accessible, and diverse contraceptive options.

When providing contraceptive counseling, several factors must be considered, including safety, availability, effectiveness, and user acceptability. The voluntary choice of contraceptive method remains a fundamental principle. Personalized counseling also enhances adherence and successful use of contraceptive techniques.

The primary purpose of birth control methods is to prevent fertilization, inhibit implantation, or stop embryonic development. Natural approaches such as abstaining from intercourse during the fertile window or using the withdrawal method offer limited protection. Other methods involve physical barriers (e.g., condoms, diaphragms, or surgical sterilization), hormonal regulation of the menstrual cycle (oral contraceptive pills), or mechanical interference using intrauterine devices (IUDs).

Oral Contraceptives (Birth Control Pills)

Oral contraceptives, commonly referred to as birth control pills, are medications taken orally to prevent pregnancy. They work by suppressing ovulation and thickening cervical mucus, which blocks sperm from reaching the egg. Birth control pills are broadly classified into two types:

1. **Progestin-only pills (mini-pills):** Contain only progestin.
2. **Combined oral contraceptive pills (COCs):** Contain both estrogen and progestin.

Combination pills are typically more effective than progestin-only pills. They are available in various pack sizes—such as 21-day or 28-day packs—and extended-cycle packs like *Seasonique*, which contain 84 active pills followed by 7 inactive pills. The inactive tablets are designed to help maintain routine use and trigger menstrual bleeding during the pill-free interval. Missing inactive tablets does not affect contraceptive protection, but consistent use of active pills is essential for efficacy.

Classification of Birth Control Pills

1. Based on Hormone Dose

- **Low-Dose Pills:** Contain 35 µg or less of estrogen, offering effective contraception with minimal side effects.
- **Examples:**
 - a. Drospirenone + Ethinylestradiol (*Yasmin*)
 - b. Levonorgestrel + Ethinylestradiol (*Levora*)
 - c. Norgestrel + Ethinylestradiol (*Lo/Ovral-28*)
 - d. Norgestimat + Ethinylestradiol (*OrthoTri-CyclenLo*)
 - e. Norethindrone + Ethinylestradiol (*Estrostep, Ortho-Novum*)
- **Ultra-Low Dose Pills:** Contain 20 µg or less of estrogen.

Examples:

- a. Norethindrone + Ethinylestradiol (*LoestrinFe*)
- b. Levonorgestrel + Ethinylestradiol (*Alesse*)
- c. Drospirenone + Ethinylestradiol (*Yaz*)

2. Based on Gender

- **Female Contraceptive Pills:**
 - **Combined Oral Pills:** Contain both estrogen and progestin; taken once daily.
 - **Progestin-Only Pills:** Contain only progestin; taken daily without interruption.
- **Male Oral contraceptive pill:** Although not commercially available, the compound *11-beta-methyl-19-nortestosterone dodecylcarbonate (11β-MNTDC)* has shown promise as an androgen–progestin combination with contraceptive potential for men.

3. Based on Hormonal Composition

A) progestin-only pill [pops] : Contain synthetic progestogens such as ethynodiol, levonorgestrel, or norethisterone. They are approximately 96–97% effective when used correctly and are suitable for women who cannot take estrogen. These pills alter cervical mucus to prevent sperm penetration and may inhibit implantation.

A long-acting injectable form, *depot medroxyprogesterone acetate (150 mg every three months)*, offers extended protection but may delay fertility return for up to 18 months after discontinuation.

Common side effects: Headaches, breast tenderness, irregular bleeding, and menstrual changes.

Examples of brands: *Errin, Camila, Heather, Jolivette, Nora-BE.*

Advantages:

- **Safe during lactation:** Does not affect breast milk production or harm infants.
- **Menstrual benefits:** Reduces uterine bleeding, menstrual cramps, and endometrial growth.
- **Migraine relief:** Decreases menstrual migraine severity.
- **Endometriosis management:** Reduces endometrial proliferation and associated pain.

B) Combined oral contraceptive pills [cocs]: These contain both estrogen and progestin. The first COC was introduced in the United States in 1957 for regulating menstrual cycles. Modern formulations use *ethinylestradiol* as the estrogen component, while progestins may include norethisterone, levonorgestrel, ethynodiol, desogestrel, or gestodene.

Third-generation progestins like desogestrel and gestodene have lower androgenic activity but a slightly increased risk of thromboembolism compared to second-generation types. The estrogen dose in most preparations ranges from 20–50 µg. Typically, pills are taken for 21 consecutive days followed by a 7-day break, during which withdrawal bleeding occurs. Fertility generally returns quickly after discontinuation.

Examples: *Azurette, Balcoltra, Beyaz, Cryselle, Gianvi, Junel, Loestrin 24 Fe, Yasmin, Yaz.*

Types of COC Formulations:

- **Monophasic:** Fixed estrogen and progestin dose in each pill; taken for 21 days with a 7-day break.
- **Biphasic:** Estrogen given for 10 days, followed by progestin for 11 days; less commonly recommended due to endometrial cancer risk.
- **Triphasic:** Hormone levels vary across three phases to mimic the natural cycle, improving tolerance and minimizing side effects.

4. Based on Generations

1. **First Generation:** Contained high levels of estrogen and early synthetic progestins (e.g., norethindrone, lynestrenol). These were associated with more side effects and are now largely discontinued.
2. **Second Generation:** Introduced in the 1970s with lower hormone levels, commonly using *levonorgestrel* and *norethisterone*. Examples include *Loestrin*, *Microgynon*, and *Logynon*.
3. **Third Generation:** Developed in the 1980s with newer progestins like *desogestrel*, *gestodene*, and *norgestimate*—offering improved lipid profiles and reduced androgenic effects. Examples include *Marvelon* and *Cilest*.
4. **Fourth Generation:** The latest formulations containing progestins such as *drospirenone*, *dienogest*, and *nomegestrol acetate*. Examples include *Yasmin* (ethinylestradiol + drospirenone), *Zoely* (estradiol hemihydrate + nomegestrol acetate), and *Qlaira* (estradiol valerate + dienogest).

Pharmacology of Birth Control Pill from Papaya Seed:[9]

- **Active Constituents:**

Papaya seeds (*Carica papaya* L.) contain several bioactive phytochemicals responsible for antifertility effects:

Alkaloids (carpaine, carpine)

Isothiocyanates (benzyl isothiocyanate – BITC)

Flavonoids

Phenolic compounds

Fatty acids (oleic, palmitic, stearic acids)

These compounds are believed to act on the reproductive system, altering spermatogenesis and hormone regulation. Mechanism of Action:[10]

- **Antispermatic effect:** Papaya seed extracts impair spermatogenesis, leading to decreased sperm count, motility, and viability. This is attributed mainly to BITC and alkaloids.
- **Hormonal modulation:** Studies suggest papaya seed extract reduces serum testosterone levels and affects testicular steroidogenesis, leading to suppression of fertility.
Membrane disruption: Benzyl isothiocyanate and fatty acids may alter sperm plasma membrane integrity, reducing fertilization capacity.
- **Reversibility:** In most animal studies, fertility was restored after discontinuation, suggesting the effect is reversible and non-permanent.
- **Pharmacokinetic:[11]**

1. **Absorption:** Active phytochemicals are absorbed after oral intake. Distribution: Constituents reach testicular tissue and reproductive organs.
2. **Metabolism:** Mainly metabolized in the liver via conjugation (glucuronidation, sulfation). Excretion: Excreted through urine and feces.

Pharmacological Effects[12]

Male contraception: Suppression of spermatogenesis, reduced sperm motility, infertility.

Female contraception (less studied): Some studies show interference with implantation due to anti-estrogenic effects.

Antioxidant/anti-inflammatory: Secondary pharmacological actions of papaya seeds.

Safety and Toxicity: Animal studies: Showed no major systemic toxicity at contraceptive doses. Human studies: -Limited; further clinical trials are needed to confirm safety, dose standardization, and long-term effects.

Papaya seeds exhibit significant pharmacological effects that suggest potential use as a natural birth control agent. The seeds contain bioactive compounds such as carpaine, benzyl isothiocyanate, flavonoids, and alkaloids, which contribute to their antifertility properties. Studies have shown that extracts of papaya seeds can reduce sperm count, motility, and viability in males, leading to temporary infertility without causing permanent damage to reproductive organs. In females, the extract may exert an anti-implantation effect by altering the uterine lining and disrupting hormonal balance, thereby preventing

fertilization or implantation of the fertilized ovum. These effects are often reversible, as fertility tends to return once the use of the extract is stopped. The hormonal modulation caused by papaya seed compounds also affects levels of testosterone, estrogen, and progesterone, further contributing to its contraceptive action. Overall, papaya seeds show promising non-toxic and reversible contraceptive potential, although most evidence comes from animal studies. Therefore, more clinical research on humans is required before papaya seed-based formulations can be considered safe and effective for use as birth control pills.

Generic Name	Example Proprietary Name(s)	Description
desogestrel and ethinyl estradiol	Apri, Azurette, Caziant, Cyred, Cyred EQ, Emoquette, others	Combination progestin and estrogen pill; some packs may be triphasic
dienogest and estradiol valerate	Natazia	Quadruphasic progestin and estrogen pill
drospirenone	Slynd	Progestin-only birth control pills ("mini-pills"); for use in breast-feeding or high risk for blood clots.
drospirenone and estetrol	Nextstellis	First contraceptive pill containing estetrol, a naturally occurring estrogen produced from a plant source. Nextstellis may be less effective in females with a BMI ≥ 30 kg/m ² .
drospirenone and ethinyl estradiol	Gianvi, Jasmie, Loryna, Nikki, Ocella, Yasmin, Yaz, Zarah, others	Drospirenone-containing birth control pills may be associated with a higher risk for rare but serious blood clots (DVT, PE) compared to other progestin-containing pills.
drospirenone, ethinyl estradiol and levomefolate	Beyaz, Safyral, Tydemy	Drospirenone-containing birth control pills may be associated with a higher risk for rare but serious blood clots (DVT, PE) than other progestin-containing pills. Contains a daily dose of folate to lower rare neural tube defect risk.
ethynodiol and ethinyl estradiol	Kelnor 1/50, Zovia 1/35	Monophasic combination progestin and estrogen pill.
levonorgestrel and ethinyl estradiol	Afirmelle, Altavera, Amethyst, Ashlyna, Aubra, and others	Combination progestin and estrogen pill; some examples are triphasic, extended-cycle pills, or continuous-cycle pill.
norethindrone	Camila, Deblitane, Errin, Heather, Incassia, others	Progestin-only birth control pills ("mini-pills"); for use in breast-feeding or high risk for blood clots.
norethindrone and ethinyl estradiol	Alyacen 1/35, Alyacen 7/7/7, Aranelle, Aurovela 1.5/30, Aurovela 1/20, others	Combination progestin and estrogen pill; some are biphasic or triphasic.
norgestimate and ethinyl estradiol	Estarylla, Femynor, Mili, Mono-Linyah, Nymyo, others	Combination progestin and estrogen pill; some options are triphasic.
norgestrel	Opill	Over-the-counter (OTC) progestin only ("mini") pill, available without a prescription in March 2024 online and on shelves at pharmacies, grocery stores and other retailers.
norgestrel and ethinyl estradiol	Elinest, Low-Ogestrel-28, Cryselle 28, Ogestrel-28, others	Combination progestin and estrogen pill

Table 1: Common Birth Control Pills.



Role of Papaya Seeds in Birth Control [10]

Papaya seeds have been studied for their natural antifertility effects, especially in males. They contain bioactive compounds that impact hormonal balance and reproductive organ function.

In Males:

Reduces sperm production (spermatogenesis inhibition)

Lowers sperm motility and sperm count

Induces temporary infertility (reversible after discontinuation) Alters testosterone levels In Females (less studied):

May disturb the menstrual cycle

Slight estrogenic or anti-progesterone effect

Could interfere with ovulation or implantation

IngredientsPapaya Seeds Responsiblefor Antifertility[11]

PHARMACOGNOSY OF PAPAYA SEED

Botanical name: Carica papaya Linn.

Family: Caricaceae

Common name: Papaya, Papita (Hindi)

Plant part used: Seeds (also leaves and latex in traditional use)

Macroscopic Characteristics Feature Description

Shape: Ovoid or kidney-shaped

Color: Black or dark brown when dried Size: ~4-5 mm

Surface: Rough and wrinkled due to sarcotesta Taste: Slightly bitter, peppery Odour: Characteristic pungent

Microscopic Characteristics

Outer seed coat: Thick sclerenchymatous layer

Endosperm: Oil cells, protein bodies Starch grains and fixed oil droplets present Stone cells may be observed

Compound	Function (as Birth Control / Antifertility Agent)
Carpaine (alkaloid)	Inhibits sperm production and reduces sperm motility.
Benzyl isothiocyanate (BITC)	Causes damage to sperm cells; decreases sperm count and viability.
Papain (enzyme)	Alters reproductive tissues and may affect implantation.
Phytosterols (β-sitosterol, stigmasterol)	Disrupt hormonal balance; may reduce fertility.
Flavonoids and Phenolic compounds	Cause oxidative stress in sperm cells leading to reduced fertility.
Fatty acids (oleic, palmitic, linoleic acids)	Support spermicidal activity and reduce sperm membrane integrity.

CHEMICAL CONSTITUTES [14,1516,17]

Class of Chemical Constituent	Key Compounds Present in Papaya Seeds	Main Functions / Properties
Alkaloids	Carpaine	Antifertility (reduces sperm motility and count), antimicrobial, cardiotonic
Isothiocyanates	Benzyl isothiocyanate (BITC), Phenylethyl isothiocyanate	Spermicidal, antifertility, anticancer, antimicrobial
Enzymes	Papain, Chymopapain	Proteolytic activity, may affect implantation, digestive aid
Phytosterols	β -sitosterol, Stigmasterol, Campesterol	Hormonal balance modulation, antifertility, cholesterol-lowering

Class of Chemical Constituent	Key Compounds Present in Papaya Seeds	Main Functions / Properties
Flavonoids	Quercetin, Kaempferol	Antioxidant, may induce oxidative stress in sperm cells
Phenolic Compounds	Caffeic acid, Vanillic acid, Ferulic acid	Antioxidant, antimicrobial
Fatty Acids	Oleic acid, Palmitic acid, Linoleic acid	Affect sperm membrane integrity, spermicidal effect
Carotenoids	β -carotene	Antioxidant activity
Saponins	—	Contribute to antifertility and spermicidal effects
Glycosides	—	Mild hormonal effects, antioxidant

Conclusion

The study of *Carica papaya* (papaya) seeds as a potential source of natural contraceptive agents presents a promising alternative to synthetic birth control methods. The presence of bioactive compounds such as alkaloids, flavonoids, and saponins contributes to their ability to reduce sperm count, motility, and viability without causing long-term toxicity or hormonal imbalance. Research findings from animal studies indicate that the antifertility effects of papaya seed extracts are reversible, suggesting potential for safe and temporary male contraception.

Developing a birth control pill derived from papaya seeds could offer a non-hormonal, plant-based, cost-effective, and eco-friendly approach to family planning. However, comprehensive clinical trials are essential to confirm safety, standardize dosage, and evaluate efficacy in humans. With further scientific validation, papaya seed-based contraceptives could represent a significant advancement in natural reproductive health management and male contraceptive options.

Result:-

Papaya seeds have been found to possess natural antifertility properties that can act as a form of birth control. Studies, especially on animals, have shown that consumption of papaya seed extract can significantly reduce sperm count and motility in males, leading to temporary infertility. In females, the extract may interfere with ovulation or prevent the implantation of a fertilized egg in the uterus. These effects are believed to be caused by bioactive compounds such as carpaine, benzyl isothiocyanate, flavonoids, and alkaloids, which influence reproductive hormones like testosterone and estrogen. The contraceptive effects of papaya seeds are generally reversible; fertility usually returns to normal after stopping their use. Although papaya seeds are considered safe in small amounts, excessive or prolonged consumption may cause toxicity, particularly affecting the liver and kidneys. In conclusion, papaya seeds can temporarily prevent pregnancy through hormonal and reproductive effects, but they are not a medically approved or reliable form of contraception and should not replace standard birth control methods.



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